VERNER WHEELOCK
ASSOCIATES LIMITED

FOOD SAFETY AND PIG PRODUCTION IN DENMARK

Controls on antibiotics, veterinary medicines and Salmonella

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The information compiled in this briefing is a distillation from a large volume of literature. Text and Tables may be cited, but the source should be acknowledged.

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

Public confidence in food products is critically dependent on maintaining high standards of food safety. This can only be achieved if newly emerging hazards are identified and strategies implemented to control those which may place consumers at risk.

In recent years the Danish pig industry has been proactive in tackling food safety issues which may present a threat to consumers of Danish pork and bacon. There has been whole-hearted commitment from all sectors of the industry coupled with support from the Danish Government to conduct research and develop programmes to ensure that any hazards are controlled effectively.

These include:

- The Danish nation-wide *Salmonella* surveillance and control system in finishing pigs which was established in 1995. By 2001, 97% of all herds producing over 200 pigs were virtually free of *Salmonella* or had a very low prevalence. The remaining herds are required to take steps which will reduce the prevalence of *Salmonella*.

- Since 1st January, 2000, Antibiotic Growth Promoters have no longer been used in Danish pig production. This is because of concerns about the development of resistance to antibiotics, which could be a serious threat to public health.

- There are very tight controls on the use of veterinary medicines in Denmark. In 1995, legislation was introduced which removed the right of veterinarians to dispense veterinary medicines and sell them at a profit. This means veterinarians no longer have any financial incentive to sell medicines. In May 2000, the Danish Ministry of Foods established a unique registration database system ~ VetStat. The primary objective is to find the relationship between the use of veterinary drugs and the development of

antibiotic resistance. The database consists of relevant details of the application of all veterinary medicines. The information produced allows comparisons to be made, for example, between farms or between veterinarians. Hence scope for reductions in use can be identified.

As a consequence the number of antibiotic-resistant bacteria in Danish pigs (and chickens) has decreased substantially. This is the first large-scale evidence that eliminating agricultural antibiotics may reverse the rise of resistant bacteria in livestock.

When these programmes are examined in a global context, it is evident that the Danish industry has progressed much further than most other developed nations involved in large-scale animal production.

The World Health Organisation has devised Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food which are essentially recommendations to reduce the overuse and misuse of antimicrobials in food animals for the protection of public health. Denmark can be regarded as a model to which other countries can aspire.

Given the growing emphasis on globalisation and the intense competition for world markets, there is no doubt that the Danish pig industry is extremely well placed.

BRIEFING

1.0 INTRODUCTION

The importance of food safety cannot be over-emphasised. Suppliers of food have an enormous responsibility to ensure that high standards of food safety are maintained. But because of rapid changes in life style, consumer expectations and methods of production, food industries have to be alert to the possibility of new hazards emerging. Many of the food scares which have occurred in recent years such as *E. coli* 0157 or BSE did not exist 20 years ago. This means that there was relatively little experience to provide a basis for coping with the hazards when they appeared.

The Danish pig industry has always aspired to the highest standards of food safety. During the past 10 years several significant initiatives have been introduced with the object of controlling possible hazards associated with bacon and pork produced in Denmark.

These are:

- Zoonoses Controls
- DANMAP (The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme: established 1995)
- Very tight controls in the use of veterinary medicines

The purpose of this report is to review progress in Denmark and to relate this to developments in other parts of the world.

2.0 ZOONOSES

Every year Denmark produces a Zoonoses Report which draws together data on the prevalence of zoonoses in humans, animals and food.

The 6th annual report for 2001 was published in 2002. It describes details of the different national programmes for the control of zoonoses and is an official publication of the Danish Zoonoses Centre and the Danish Veterinary and Food Administration. The 2001 Report is available on: www.Vetinst.dk.

2.1 Salmonella

All major food animals and food of animal origin are monitored continuously for *Salmonella*. The resulting collection of 10-20,000 *Salmonella* isolates per year is serotyped and isolates of *S. typhimurium* and *S. enteritidis* are phage typed. A comparison of *Salmonella* types isolated from food animals and food with isolates from humans makes it possible to produce estimates of the number of human cases attributable to certain animal sources. In 2001 the registered number of human salmonellosis caused by zoonotic serotypes was 2,918 (54.5 cases per 100,000 inhabitants). This number represents a continued decline from 1997 when 5,015 cases were registered.

2.1.1. Feed stuffs

All Danish feed compounders are routinely monitored for *Salmonella* by the Danish Plant Directorate. This includes routine sampling of compound feeds during feed processing and from feed materials, including raw materials of animal origin. The Danish Plant Directorate collects samples of feeding stuffs from the production plant and retailers. The number of samples depends on the size of the production, but is increased if *Salmonella* is detected in samples other than raw materials.

2.1.2 Meat

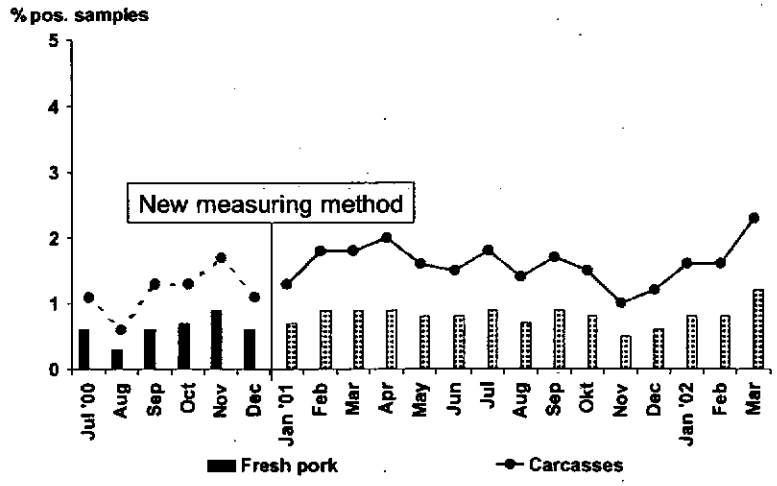
A continuous programme for the monitoring of *Salmonella* in pork at the slaughterhouses was initiated in July 1993. For each slaughterhouse the number of samples collected was determined by the actual number of animals slaughtered, approximately 2,250 samples were analysed every month.

The method of *Salmonella* monitoring was changed on 1st January 2001. It is now based on swabs taken from 5 carcases at each slaughterhouse sampled at random. The analysis is done on the pooled samples. The new system is twice as sensitive as the old system, and consequently more *Salmonella* positive carcasses are detected. The new system is equivalent to that required by the USDA for suppliers to the US market. It also has the advantage that each carcase is tattooed with the herd specific number, which makes it possible to trace each sample back to the herd of origin. (L.L. Sørensen *et al.* Salinpork 2001)

In 2000, using the old system, the proportion of *Salmonella* positive units of pork varied between 0.4% and 1.5% with a mean of 0.8% which is slightly lower than in 1999 (1.0%).

In 2001, using the new system, the number of positive carcass samples varied between 0.9% and 1.7% with a mean of 1.3%. This is comparable to 0.65% in the old system.

Salmonella in fresh pork vs. Salmonella on carcasses



Danske Slagterier 2002

In 2000, the registered number of human Salmonellosis caused by zoonotic serotypes was 2,308. Thus, the incidence in 2000 fell by 29% compared with 1999 (3,268 cases) (DANMAP, 2000).

2.2 Multi-drug resistant *Salmonella typhimurium* DT104

2.2.1 Control in primary production

In October 1997, the Danish Veterinary and Food Administration (DVFA) issued an order making the detection of multi-drug resistant *Salmonella typhimurium* DT104 notifiable in pig and cattle herds. Infected herds are put under official veterinary supervision including special hygiene at slaughter, and there is epidemiological investigation of the herd and its trade contacts. Two negative herd examinations at 45 day intervals are required to lift the sanctions. Sanctions can also be lifted if the herd is destroyed. The order was issued to prevent spread of DT104 between herds as well as from animals to humans. In August 1999, the order was replaced with a new order extending the authorities powers to investigate the spread of DT104. According to this, all animal species on an infected farm and herds associated with the infected herd by, e.g. trade of live animals or geographical location, can be ordered to be examined.

The pig industry's strategy of stamping out infected pig herds as described in the Annual Report 1999 was terminated in June 2000, as a rapidly increasing number of infected pig herds made this approach no longer economically viable.

So a new strategy has been devised which was first implemented in December 2000. By July 2002, 70 pig herds have been involved in the new approach. When DT104 is detected, movement of animals is controlled by a Zoonosis Restriction order. An intervention plan to control the disease must be introduced. The procedures relate to feed, management, health conditions, cleaning and disinfection, internal and external infection-barriers including rodent control and special handling of slurry and manure. The animals are monitored for the presence of DT104. It has been shown that in finisher herds a farm can usually be declared "free" six months after the initial detection of DT104 if the intervention plan is followed carefully.

A new measure to decontaminate carcases with *Salmonella* DT104 has been introduced. This involves washing pig carcases immediately after slaughter so that any *Salmonella* on the surface are removed. It has been established in Denmark that water at 80° C for 15 seconds causes a huge reduction in *Salmonella* contamination. This is in contrast to the procedures in Australia and the US, where the practice is used routinely but the water does contain an additive such as lactic acid or proponic acid. (V. Møgelmose, J. Bagger, B. Nielsen & D.L. Baggesen ~ Salinpork 2001)

In Denmark, the regular testing programme shows that 80-90% of all herds are free of *Salmonella*, so the hot water treatment is restricted to the 10-20% of herds, which may be contaminated with *Salmonella*.

Pigs from DT104-infected herds can be included in the human food chain but must be slaughtered under special hygienic conditions

2.2.2 Occurrence in primary production

A total of 130 pig herds have been found to be DT104 positive since 1996, constituting 0.6% of all pig herds in Denmark. From 1996 to June 2000, 60 herds were stamped out, and from July 2000 to July 2002 70 herds have followed the new DT104 reduction programme. The number of herds infected with DT104 increased markedly in 2001, when 43 new herds were identified. By July 2002, 30 herds were under a Zoonosis Restriction order.

2.2.3 Occurrence in imported meat

Of the 36,460 carcasses sampled in the national Danish *Salmonella* programme at the slaughterhouses during 2001, only 2 pooled swab samples tested positive for DT104. The prevalence of DT104 positive carcasses has been estimated to be less than 0.01%.

During 2001, the following samples of imported fresh meat were examined:

- 2,070 samples of poultry meat, 404 (19.5%) positive for *Salmonella*, 3 (0.1%) samples positive for DT104;
- 451 samples of pork, 25 (5.5%) positive for *Salmonella*, 2 (0.4%) samples positive for DT104;

- 726 samples of beef, 4 (0.6%) positive for *Salmonella*, 0 (0%) samples positive for DT104.

2.2.4 Occurrence in humans

In 2001, there were 589 cases which compare with 584 cases in 1999. However, the proportion of DT104 phage types has increased from 7% in 1997 to 14% in 2001. The increase is mainly due to imported meat and travel associated cases.

2.3 VTEC 0157

The problem of zoonotic *E. coli* infections remains low in Denmark, and no general food-associated outbreaks have been identified. Before 1997, VTEC was rarely looked for in humans. In 1997, laboratories examining more than two-thirds of the stool cultures performed in Denmark changed their diagnostic practice, and started looking for VTEC in all stools from patients with grossly bloody diarrhoea and in all stools from patients of 4 years of age or less with a history of bloody diarrhoea. Additionally, stools from patients evaluated for travellers or persistent diarrhoea have been cultured for VTEC. This approach resulted in the identification of a total of 92 VTEC infections in 2001 compared with 51 in 1999. Before 1997, approximately 5 cases were diagnosed annually. Pig meat is not known to be associated with any of the human cases.

2.4 Campylobacter

The incidence of human Campylobacter infections increased from 4,386 in 2000 to 4620 cases in 2001 (86 cases per 100,000 inhabitants). This is the highest registered incidence in Denmark. There is no apparent explanation for the emergence of Campylobacter, which remains a major cause of concern for public health. It is estimated that approximately 80% of the Campylobacter infections are domestically acquired.

2.5 Enterococci

Enterococci and *E. coli* have been chosen as indicator bacteria because they may be readily isolated from normal populations of food animals and humans, as well as from food, and because they respond to selective pressure by antimicrobials. Accordingly, they provide a measure of the occurrence of resistance in the population as a whole.

The occurrence of resistance to antimicrobial growth promoters among *E. faecium* from broilers and pigs has been monitored since the last quarter of 1995 when the DANMAP programme was initiated.

A significant decrease in resistance to virginamycin, erythromycin, nitrofurantoin, quinupristin/dalfopristin and tetracycline has been observed among *E. faecium* from pigs in 2001 compared to 2000 (DANMAP 2001).

Similarly, in 1995 20% of porcine *E. faecium* were resistant to avoparcin compared to just 3% in 2001.

Resistance to avoparcin among isolates from broilers has declined from 82% in 1995, the year avoparcin was banned in Denmark, to 5% in 2001. This finding is statistically significant. It seems likely that there is an association between the discontinued use of growth promoters and the decrease in resistance.

3.0 SALMONELLA CONTROL PROGRAMME

The Danish Salmonella surveillance and control system in finishing pigs is a nation-wide programme established in 1995.

The increase in the incidence of human salmonellosis along with a *S. infantis* outbreak prompted the Danish authorities to launch a nation-wide *Salmonella* control programme in the pig industry. The programme involves control of *Salmonella* in feedstuffs, and surveillance and control in breeding, multiplying and finishing pig herds.

3.1 Finishing Herds

The objective of the programme is to reduce the level of *Salmonella* in pork. In August 2001, a number of changes were introduced.

First, herds producing less than 200 pigs for slaughter per year are no longer included in the surveillance. However, the programme still applies to over 98% of all pigs produced.

Second, the level at which the serological test is considered positive was reduced, resulting in twice as many sero-positive results as before.

Third, the categorization of the herds continues to be based on the proportion of sero-positive meat juice samples during the last 3 months, but the results are now weighted (0.2:0.2:0.6) so that the emphasis is placed on the most recent month.

Over 600,000 samples are analysed every year, and herds are assigned to one of three levels.

Level 1 ~ a herd with no or few reactors where intervention is not required. In 2001, 97.3% of herds were allocated to this category;

Level 2 ~ a herd with a higher proportion of reactors, a reduction plan is recommended;

Level 3 ~ the proportion of reactors in the herd is unacceptably high, a reduction plan is recommended.

The prevalence of Salmonella in Danish pork is shown in Table 3.0.1.

Table 3.0.1 **Incidence of Salmonella in pork samples**

Year	% Positive
1996	1.2
1997	1.1
1998	1.2
1999	0.9
2000	0.7
2001	1.3*

*A new system of *Salmonella* monitoring was introduced on 1st January 2000. This value is equivalent to 0.65% under the old system (see 2.1.2.).

(Annual Report on Zoonoses in Denmark 2001)

Herds in Level 3 have a penalty charge of 4% deducted from the payment for each pig at slaughter. From August 2001, a charge of 2% has been imposed on Level 2. The object of these charges is to provide a financial incentive for the pig farmers to take the necessary corrective action. In practice, the abattoir uses the money to defray the additional costs incurred on the slaughter of pigs in Levels 2 and 3.

3.2 Feedstuffs

The control of feedstuffs requires heat treatment at 81° C to eliminate *Salmonella*. In addition there must be microbiological analysis of the final product and of samples taken from critical control points during production. Between 1999 and 2001, the proportion of positive samples has declined from 0.4% to 0.2%.

3.3 Breeding and multiplier herds

Each month, all herds are blood sampled and examined for *Salmonella* antibodies. Based on the level of antibiotics, a *Salmonella* index is calculated. If the index exceeds 5, pen faecal samples must be taken for the presence of *Salmonella spp*. When the index exceeds 15, a sales ban on breeding pigs is imposed until the index falls below 15.

3.4 Weaners

If a sow herd sells weaners to a *Salmonella* level 2 or 3 finishing herd (see 3.1 above), pen faecal samples must be taken and examined for the presence of *Salmonella spp*.

4.0 DANMAP

4.1 Background

A general increase in antimicrobial resistance among pathogenic bacteria is causing world-wide concern that the widespread use of antimicrobial agents in

animal production may promote resistant bacteria or resistance genes that can be transferred to bacteria pathogenic to humans. In the interests of consumer safety and the health of animals and humans, the Danish Ministers of Agriculture and Fisheries and Health in 1995 asked the Danish Veterinary Laboratory, Danish Food Agency, and Statens Serum Institut to set up a collaborative programme for the surveillance and research of antimicrobial resistance.

4.2 Objective

The programme is entitled, 'A Danish Integrated Antimicrobial Resistance Monitoring and Research Programme' (DANMAP) and the objectives are to:

- monitor the occurrence of antimicrobial resistance in bacteria in livestock animals, food and humans;
- monitor the consumption of antimicrobials for humans and animals;
- detect and quantify the spread of resistant bacteria and resistance genes from animals to man;
- provide guidelines for medical and veterinary antimicrobial chemotherapy to ensure that antimicrobials continue to be used prudently;
- publish reports annually.

4.3 Principle

The surveillance system compares resistance patterns in bacteria (identified at species level) isolated from livestock, food and humans, using identical or comparable methods. The bacterial isolates constitute representative sub-samples of the populations investigated.

Bacteria are identified to species level because different species may differ in their intrinsic resistance or tendency to develop resistance to antibiotics. Bacterial species also differ in their animal reservoirs, and therefore in their exposure to antimicrobials.
Both pathogenic and indicator bacteria are monitored. Bacteria suitable as indicators are those which are frequently isolated from a broad range of healthy animals hosts and other sources. They are included to enable levels of resistance of the same bacterial species to be compared. This system provides the basis for estimating levels of resistance in animals and humans and, by comparing these with the levels found in food, estimating the extent to which resistance is spread from animals to man.

4.4 Surveillance of Resistance in Bacteria Isolated from Humans

The National Statens Serum Institute is responsible for the surveillance of resistance among pathogens and indicator bacteria isolated from humans and for relating this to the use of antibiotics for the treatment of human infections.

A system has been established to collect representative samples of pathogenic bacteria (*E. coli; E. cloacae; Klebsiella pneumoniae; Haemophilus influenzae; Pseudomonas aeruginosa; Neisseria menigitidis; Staph. aureus;* coagulase negative *Staphylococci; Streptococcus pyogenes; Strept. pneumoniae; Strept. haemolyticus and enterococci*) from diagnostic laboratories and zoonotic bacteria (*Salmonella; Campylobacter coli/jejuni; Yersinia enterocolitica* and *Listeria monocytogenes*) isolated from clinical specimens submitted for diagnosis.

Currently plans for a system to collect a continuous and representative healthy population sample are under development, based on the results of this investigation.

4.5 Surveillance of Resistance in Bacteria Isolated from Food

The Danish Food Agency is responsible for monitoring the occurrence of antimicrobial resistance in foodborne bacteria.

The surveillance is based on:

- indicator bacteria (*E. coli, Enterococcus faecalis* and *E. faecium* are part of the microflora of several types of food and are often used as parameters of food hygiene);

- zoonotic bacteria and human pathogens (*Campylobacter coli/jejuni*; *Yersinia enterocolitica*; *Salmonella*; *Staph. aureus* and *L. monocytogenes).*

The following types of raw food are monitored: beef, pork, chicken, egg, milk products, fish, vegetables and fruit. The bacteria are isolated according to a specified plan at 12 regional centres for food inspection and shipped to the Danish Food Agency, where the identification is verified and the susceptibility to antimicrobial agents determined. Isolates are monitored for resistance against growth promoters and therapeutic antimicrobial agents.

4.6 Surveillance of Resistance in Bacteria Isolated from Livestock

The Danish Veterinary Laboratory is responsible for monitoring the occurrence of antimicrobial resistance in livestock and for relating this to the use of antimicrobial agents in livestock.

Bacteria for resistance testing are collected continuously and represent:

- animal pathogens (the bacteria most commonly associated with disease in Denmark. The isolates are collected from samples submitted for diagnosis. Animal pathogens included at present are: *Actinobacillus plueropneumoniae; S. hyicus; S. aureus* and coagulase negative *Staphylococci*);

- zoonotic bacteria (*Salmonella, Campylobacter coli/jejuni and Yersinia enterocolitica*);

- indicator bacteria (*E. coli* and *enterococci*).

The zoonotic and indicator bacteria are isolated from faecal specimens collected from calves, pigs and broilers when slaughtered. 200 specimens are collected from pigs and broilers and 75 from calves every 3 months. Samples are collected by meat inspection staff according to a stratified, pseudo-random scheme in slaughterhouses all over the country, in proportion to the number of animals slaughtered.

Bacterial isolates are tested for resistance against antimicrobial growth promoters and therapeutic antimicrobial agents. Resistance testing is performed using minimum inhibitory concentration determinations.

From 1996 to 1999, the level of tetracycline resistance in *S. typhimurium* isolates from pigs was almost constant. However there was a significant increase in tetracycline resistance from 14% in 1999 to 25% in 2000 and to 30% in 2001. This increase in resistance coincided with a 72% increase in usage of tetracycline in pigs during the same period.

From 1998 to 2001, resistance to nalidixic acid in *C. coli* from pigs decreased significantly from 17% to 5%. This decrease coincided with the withdrawal from the market of an oral fluoroquinolone formulation for pigs.

Between 1998 and 1999, the use of tylosin for growth promotion decreased considerably. As a consequence, the erythromycin resistance to *C. Coli* declined from over 60% to under 40% in 1999. However, macrolides are still used for treatment of infections in pigs. In 2000 and 2001, 8,900 kg and 10,836 kg of tylosin respectively were used. Erythromycin resistance in *C. coli* remained at relatively high levels during 1999 – 2001.

The resistance levels for the indicator *E. coli* have remained about the same as in 2000. Even though the consumption of tetracycline in weaner pigs increased markedly between 1999 and 2000, this has not caused any change in the tetracycline resistance in *E. coli* from pigs at slaughter. The *E. coli* serotypes causing diarrhoea in weaner pigs are different from the serotypes that predominate in older pigs. In 2001, only very small proportions of the total quantities of aminoglycocides and sulphonamides used in pigs were administered to slaughter pigs. In spite of this, streptomycin and sulphonamide resistance are often seen in combination with tetracycline resistance and use of tetracycline may have co-selected for streptomycin and sulphonamide resistance. (DANMAP 2001 p41).

Since 1995, there have been significant reductions in the amounts of antibiotics used in Danish animal production. The Danish Veterinary Laboratories have studied the impact of these changes on the incidence of resistance in a number of different bacteria. The results demonstrate that it is possible to reduce the occurrence of antimicrobial resistance in a national population of animals when the selective pressure is removed.

Full details of the results have been published in "Effects of Abolishment of the Use of Anti-microbial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Faecal Enterococci from Food Animals in Denmark" by Frank Aarestrup and colleagues[1].

5.0 ANTIBIOTIC GROWTH PROMOTERS

In 1998 the Danish food animal industries adopted a voluntary ban on the use of antimicrobial growth promoters (AGPs). As from the 31st December, 1999, AGPs have not been used in the production of pigs in Denmark.

The sequence of events leading to the ban began in 1979 with the debate on the value of macrolides, tylosin and spiramycin as growth promoters which focused on productivity issues such as profit and loss. Subsequent investigations demonstrated that improved efficiency in production was found when the antibiotics were used in weaner and finisher feeds.

Throughout 1994 and 1995 the debate on agricultural use gathered pace and was extended to include the potential effects on human health. Several experts suggested that the use of AGPs in animal production could contribute to the development of bacterial resistance to antibiotics used for the treatment of infections in humans. In Denmark more and more people, particularly politicians, questioned the justification for the use of AGPs in 'healthy animals'.

April 1995 was a watershed. The Danish Veterinary Laboratory published evidence showing that avoparcin could cause resistance and cross-resistance to vancomycin. The National Committee for Pig Breeding, Nutrition, Health and Production (National Committee) immediately took the decision that producers should cease to use avoparcin as a growth promoter in pig feeds. It also recommended that AGPs should not be used in finisher feeds. This led to a reduction of approximately 40% in the consumption of growth promoters contained in finisher feeds.
During the second half of 1997 the public debate continued, culminating in a television broadcast which stimulated much political discussion on the justification for using AGPs in pig feeds. The National Committee recognised the potential negative consequences of the debate and decided to abolish the use of AGPs in finisher feed for pigs over 35 kg. This key decision by the National Committee has led to an agreement, by essentially all producer members of the Danish co-operative slaughterhouses which handle over 95% of all pigs, to implement the ban.
In the Autumn of 1998 the National Committee decided to prohibit the use of AGPs in weaners from 1st January 2000. This voluntary agreement with producers was based on the following three principles:

1. From 1st March 1998 antibiotic and chemotherapeutic growth promoters must not be used in feed for finishing pigs over 35 kg.

[1] Aarestrup, F. *et al* (2001) *Antimicrobial Agents and Chemotherapy*: 45 (7) pp 2054-2059

Farmers who do not comply are required to pay a fine of Dkr 0.20 per pig.

2. Producers must agree to random testing and allow the slaughterhouse to inspect the herd and take necessary feed samples for testing.

3. If a producer violates the agreement, then the fine of Dkr 0.20 (about 2p) per kilo dead weight on pigs is levied, for the period in which AGPs have been used (a minimum of 3 months applies).

Effectively, this means that all producers ceased using AGPs.

5.1 CONVERSION STRATEGIES

When AGPs were removed from the finishers there were few problems and these were readily overcome with existing knowledge. However there were more difficulties with the weaners. Specifically these were:

- Lower weight at transfer;
- More cases of diarrhoea requiring treatment;
- More variations in weight at the time of transfer.

Research has established that the problems can be alleviated by restricting the feed to 75% of the *ad libitum* consumption and feeding 4 times per day. With this regime, there is a reduction in the incidence of diarrhoea.

Presently, research into AGP alternatives is being conducted. Results found so far include increased productivity and improved enteric health by the incorporation of organic acids into feed or water. Alternatives such as probiotics and oligo-saccharides have shown disappointing results, but the research continues.

The National Committee for Pig Production has been collecting evidence from 62 finisher herds since 1995. The results are shown in Table 5.1.1 below. AGPs were first removed in 1998. Although there was a very small increase in mortality, the improvement in growth rate has been maintained.

Table 5.1.1: National average for production efficiency control - finishers

	April 1995 - April 1996	**April 1996 - April 1997**	**April 1997 - April 1998**	**April 1998 - April 1999**	**April 1999 - April 2000**	**April 2000 - April 2001**
Daily Gain, g	744 -	762 (+18 g)	778 (+16g)	786 (+8g)	798 (+12g)	817 (+19g)
Mortality %	3.0	3.2	3.2	3.4	3.6	3.4

(Danske Slagterier 2001)

Table 5.1. 2: National average for production efficiency control - weaners

	April 1995 - April 1996	April 1996 - April 1997	April 1997 – April 1998	April 1998 - April 1999	April 1999 - April 2000	April 2000 - April 2001
Daily Gain, g	422	420	419	427	407 (-20g)	411
Mortality %	2.7	2.8	2.9	2.9	3.6 (+0.7)	3.5 (-0.1)
Age at 30 kg, days	82.6	82.6	82.8	82.9	85.3 (+2.4)	85.5

(Danske Slagterier 2001)

The corresponding values for the weaners (Table 5.1.2) shows that when AGPs were removed (April 1999-2000) there was an increase in mortality and in the time taken to reach 30 kg. The removal of AGPs has enhanced a number of fundamental problems:

1. Post-weaning diarrhoea
2. Chronic infections (*Lawsonia intracellularis*)
3. Nutritional overload
4. Utilisation of nutrients in the feed

The Danish industry is determined to overcome these difficulties without resuming the use of AGPs.

A number of different strategies are being investigated. These are:

- Management Factors

  ⇒ All-in All-out systems with Weaning to Finish in the same pen;

  ⇒ Improving the environment by close attention to the ventilation systems to avoid exposure to draught, cold and humidity;

  ⇒ Avoidance of overcrowding;

  ⇒ Unnecessary removal of pigs that are less than 24 hours old results in greater uniformity of weight.
- Nutrition

  ⇒ Restrictive feeding during the first 14 days post-weaning can improve pig health compared to *ad libitum* feeding;

  ⇒ Use of additives. Over 100 products have been tested, for example, the use of copper at 90 mg/kg was shown to have a positive effect;

  ⇒ Protective diets with a low protein content but a high proportion of animal protein may reduce the prevalence of diarrhoea;

⇒ Fermented liquid feed, as this can be a cheap way to add lactic acid.

By using a combination of the above approaches, an optimised management system can be devised, which experience shows can help to alleviate the problems which arise when AGPs are not used in weaners.

It is likely that future results will improve by optimised feed composition and management. Fermented liquid feed for weaners, growers and finishers under laboratory or semi-laboratory conditions has shown promising results. Clinical trials, under field conditions, show the least consistent results, hence the need to improve such techniques for field use. This research aims to find out how to achieve a healthy gut condition by feed and feeding practices.

The withdrawal of AGPs from the diet has stimulated considerable interest in the role of diet in the control of pathogens. A detailed review was presented at a meeting of the Nutrition Society in June 2000 by Bach Knudsen[2] of the Danish Institute of Agricultural Sciences. This was entitled, "Development of antibiotic resistance and options to replace antimicrobials in animal diets". He noted that there is increasing evidence that the feed structure, which relates to the type of plant material in the diet and the way it is processed, can be used to reduce *Salmonella* prevalence at the herd level. However he stressed that using the diet to manage gut health is not straightforward, since the expression of a pathogen in many cases requires the presence of the components of the commensal biota.

A comparison of a wheat-based diet, fed as meal or in pelleted form, found that productivity was higher with pellets, but the risk of *Salmonella* infection was reduced from 30% to 10% when fed as meal. It has been suggested that pigs fed meal have gastric contents which are easily distributed whereas there is a tendency towards phase separation when fed pellets. The consistency with the meal feed may stimulate lactobacilli which produce organic acids. Bacteria such as *Salmonella* are sensitive to the low pH and so are less likely to survive. (Salinpork 2001)

6.0 CONTROLS ON THE USE OF VETERINARY DRUGS

Dispensing of Medicines

In Denmark there are very tight controls on the use of veterinary medicines. In 1995, legislation was introduced which removed the right of the veterinary surgeon to dispense veterinary medicines and to sell them at a profit.

Virtually all veterinary medicines used in therapy are Prescription Only Medicines (POMs) and must be distributed through pharmacies. The pharmacy sells medicine either to veterinarians for use in their practice, or directly to the farmer upon presentation of a prescription. Veterinarians have no financial incentive to sell medicines as the law limits the mark-up.

[2] Knudsen, K.E.B. *et al* (2001) *Proceedings of the Nutrition Society*: 60 (3) pp 291-299

Immediately after the change in legislation there was a sharp fall in the amounts of antimicrobials used (see Table 6.1).

6.1 Consumption of Antimicrobials

In Denmark, detailed information on the use of antimicrobials is collected from the pharmaceutical industry. Table 6.1.1 presents data going back to 1988.

Table 6.1.1: Trends in the Consumption of Antimicrobials for Treatment of Food Animals (kg active compound)

	1988	1990	1992	1994	1996	1997	1998	1999	2000	2001
Tetracyclines	3,600	9,300	22,000	36,500	12,900	13,700	12,100	16,200	24,000	27,900
Penicillins	3,800	5,000	6,700	9,400	7,200	13,100	14,300	14,700	14,800	17,100
Semisyn.Pen.etc	1,000	1,200	2,500	4,400	5,800	6,200	6,700	6,600	7,600	9,300
Sulfa / TMP	2,200	3,800	7,900	9,500	4,800	6,900	7,700	6,800	7,000	7,400
Sulphonamides	24,000	8,700	5,900	5,600	2,100	1,400	1,000	1,000	1,000	800
Macrolides	9,300	10,900	12,900	11,400	7,600	6,700	7,100	8,700	15,400	19,500
Aminogycosides	7,400	7,700	8,500	8,600	7,100	7,000	7,800	7,500	10,400	11,900
Others	6,900	6,700	6,800	4,400	600	650	650	350	300	300
Total	58,400	53,400	73,200	89,900	48,100	55,700	57,300	61,900	80,600	94,200

N.B. Figures excluded from the statistics are antimicrobials used in aquaculture or in companion animals. [*Note: 'Others' include the group Fluoroquinolones*]

(DANMAP 2001)

Key Points:

- Consumption of antimicrobials in food animals has increased by over 50% between 1998 and 2000;
- Tetracyclines are the main causative agents for this increase which doubled between 1998 and 2000;
- It is possible that this increased usage of tetracyclines could be explained by the voluntary withdrawal of AGPs in pigs which may have increased the intestinal disorders in the pigs;
- Assuming all the antimicrobials recorded for farm animals were used in pigs, then the average per pig would have been 3.6g. This is obtained by relating the total 80.6 tonnes to the 22.4 million pigs produced in 2000.
- Fluoroquinolones have seen a marked decrease of more than 50% in the last 2 years. (Table 6.1.2). Consumption of fluoroquinolones in food animals is a concern, especially as these are the initial antimicrobials prescribed in hospitals to treat patients with gastro-enteritis.

- The Danish guidelines for the prudent use of antibiotics recognise that because of concerns about resistance, fluoroquinolones should not be first choice for treatment of infections in animals. In 1998, the Danish Veterinary and Food Administration recommended that all veterinarians should exercise restraint in the prescription of fluoroquinolones. In 1999, the manufacturer of enrofloxacin withdrew the product, which was widely used in premix for pigs. As a consequence the usage has fallen substantially ~ from just over 400 kg active ingredient in 1998 to under 150 kg in 2000 (Table 6.1.2). There was a small increase again in 2000. The decreasing use in pigs is reflected in the reduction in resistance of *E. coli* 0149 isolated from young pigs with diarrhoea.

Table 6.1.2: Usage of quinolones for the treatment of food animals.

Year	Total kg
1996	400
1997	450
1998	400
1999	150
2000	170
2001	200

Table 6.1.3: Consumption of Antimicrobial Growth Promoters (kg active compound) Denmark 1990-2000
1989-1999 data collected by the Danish Plant Directorate

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
Bactracin	3983	3675	5657	10636	13689	7910	8399	8544	3945	63	0
Flavomycin	494	1021	1299	415	77	48	18	93	6	665	0
Avoparcin	13718	23153	17210	19572	24117	5690	0	0	0	0	0
Monensin	2381	2532	3700	4451	4755	5007	4741	3008	935	0	0
Salinomycin	12	0	0	1224	213	850	759	460	113	0	0
Spiramycin	0	0	0	0	95	507	15	3	0.3	0	0
Tylosin	42632	33189	26980	27986	37111	52275	68350	62009	13148	1827	0
Avilamycin	10	180	853	132	433	1665	2740	670	7	91	0
Carbadox	850	3195	7221	15536	10012	1181	1985	4153	1803	293	0
Olaquindox	11391	23665	21193	16871	22483	16213	13486	17595	28445	9344	0
Virginiamycin	3837	3704	15537	12262	2801	2590	5055	10644	892	0	0
Total	79308	94314	99650	109085	115786	93936	105548	107179	49294	12283	0

(DANMAP 2000)

Note: According to VetStat (see 6.3) very small quantities of flavomycin (11kg) and avilamycin (3kg) were used in 2001. These are among the 4 growth promoters still approved for use in the EU.

The key points from Table 6.1.3 are:

- These data confirm that during 2000 no AGPs were used in Denmark;

- This compares with a value of over 100 tonnes used in 1997;
- Although there has been some increase in the therapeutic usage of antimicrobials, the total for 2000 was less than 50% of that used in 1997.

This is the last year in which data is being collected from the pharmaceutical industries. In future, data collected through VetStat (see 6.2) will be used.

EU Commission

The EU Commission Scientific Steering Committee on Microbial Resistance published its opinion in May 1999.

It concluded that the use of antimicrobials as growth promoting agents from classes which are or may be used in human or veterinary medicines should be phased out as soon as possible and ultimately abolished. It also emphasised to feed manufacturers and farmers that the continuous feeding of antimicrobial growth promoters for the purpose of disease prevention is a contravention of EU regulations.

In March 2002, the Commission announced proposals which will phase out the use of the last 4 antibiotics which are still allowed as growth promoters in animal feed. These are monensin sodium, salinomycin sodium, avilamycin and flavophospholipol. The licenses will be withdrawn in 2006 if current proposals are accepted.

6.2 VetStat

VetStat collects data on usage of all prescription medicines prescribed or used by veterinarians, including human medicines. VetStat also collects data on usage of antimicrobial growth promoters and coccidiostats.

Collection of data

All antimicrobials for treatment of disease are prescription-only medicines which are available only through pharmacies. Antimicrobials obtained by veterinarians for use in practice or for re-selling to clients must also be purchased through pharmacies. The only exception to this is pre-mixes for use in medicated feed produced at licensed feed mills. A farmer may obtain such feed on the basis of a veterinarian's prescription. However, the feed mill may obtain the pre-mix directly from a medical wholesaler or a pharmaceutical company. Data in VetStat originates from three sources: pharmacies, large animal practices and feed mills.

Pharmacies

Information for use in VetStat is extracted automatically during electronic processing of sales at the pharmacy, be it medicine ordered by a veterinarian for use in practice or a sale based on a veterinary prescription redeemed by

an animal owner. The data record describing each sale includes a numerical code unequivocally identifying the type of medicine, including its formulation, strength and size of pack; the quantity sold of each pack; codes for target animal species, age group and disease entity as stated on the prescription (the two latter for production animals only); where applicable, a code identifying the farm where the medicine will be used; codes identifying the prescribing veterinarian, the date of sale, as well as other items of information. For medicines sold for use in practice, the type and quantity of medicine as well as the receiving practice is identified.

The data are sent electronically on a monthly basis to the Danish Medicines Agency which forwards them to the central VetStat database.

Veterinary Practices

Veterinarians are required by law to report to VetStat the use of all prescription medicines in production animals. The information to be reported includes the identity and quantity of medicine, target animal species, age group and disease entity, farm ID, as well as information identifying the veterinarian and the practice. Veterinarians are not presently required to report usage of medicines in companion animals and horses.

For data collection, most practices use software that automatically extracts the information required by VetStat during the billing procedure. In this case, there is no special data entry required.

Veterinarians also have the option of recording usage directly into the VetStat database, which can be accessed via the internet.

Feed Mills

Feed mills record sales of medicated feed directly into the database via the internet. The information recorded includes a code identifying the active ingredient, its concentration, the quantity of feed, as well as information identifying target species, age group, the farm and the prescriber. For coccidiostats, records identify the type of coccidiostat, the concentration, the quantity of feed sold, and the identity of the farm receiving it. The records are sent electronically to the VetStat database once a month.

Access to data

Veterinarians and farmers may access their data via a secure connection to the VetStat homepage on the internet. Their access is restricted by password to registrations concerning their own clients or herds respectively. However, for comparative purposes, they have access to standardized outputs showing mean usage on other farms on a regional and national level. In order to make such comparisons meaningful, they have defined Animal Daily Dosages (ADD) for each combination of antimicrobial product and animal species/age group. An ADD is, for any formulation, the daily dosage required to treat an animal of a certain weight. They have used the manufacturers recommended

dosages and when these have been given as a range they have chosen the median value. They have also, for each species and age group, chosen a standard weight for each animal. So, for a given antimicrobial, they have the total quantity active compound recorded as used for a species and age group and divide by the median dosage in mg/kg and divide again with the standard weight chosen.

Pharmacies and the veterinarians started to collect data on 1 May 2000 and 1 July 2000 respectively. The feed mills also started reporting on 1 July 2000. During the first year, about 75,000 records per month were received from pharmacies, about 40,000 from veterinarians and about 2,000 from feed mills. Data validation procedures and reporting tools are being developed.

6.3 Comparison of pharmaceutical data with VetStat

In 2001, the total quantity of antimicrobials reported by pharmaceutical companies amounted to 97,400 kg. This value is higher than that shown in Table 6.1.1 because it includes use in aquaculture. It excludes preparations obviously intended for use in pigs. By contrast, the corresponding data from VetStat amounted to only 96,200 kg. It has been established that some of the discrepancy has arisen because one pharmaceutical company erroneously reported some antimicrobials as having been sold for domestic use, even though they were actually exported. VetStat has also shown that in 2001, very small quantities of flavomycin (11 kg) and avilamycin (3 kg) were used. These are among the 4 growth promoters still approved for use by the EU.

Pigs

About 76% of antimicrobials from the pharmacies and 38% in the medicated feed are for use in pigs. (Tables 6.2.1. and 6.2.3.). Using the production figures for 2000, this is equivalent to about 41 mg/kg of meat produced.

Table 6.2.1: Antimicrobials sold from pharmacies in Denmark for use in pigs

Pigs	Kg active ingredient	%
Breeders and suckling pigs	18,617	
Weaners	27,919	
Slaughter pigs	22,028	
Age not given	854	
Total all pigs	69,418	76
Total all animals	91,602	100

Table 6.2.3: Sales of antimicrobials as medicated feed for use in pigs

Pigs	Kg active ingredient	%
Breeders and suckling pigs	145	
Weaners	1,476	
Slaughter pigs	141	
Total all pigs	1,762	38
Total all animals	4,646	100

Initially the information is being updated once a month, but it will be possible, at a later stage, to update the database on a daily basis if required. VetStat will enable farmers and veterinarians to compare their own data with statistical information. Therefore, the consumption data can be used as a farm management tool. The register will form the basis of pharmaco-epidemiological studies, including the analysis of prescription habits, on the consumption of medicine in relation to animal species, age of animals and diagnosis and the examination of the association between usage of antibiotics and resistance. The ultimate objective is to minimise consumption and to optimise usage in Danish farm animals.

7.0 WHO GUIDELINES

WHO has agreed a series of criteria which should be incorporated by national governments into a pro-active approach to reduce the need for antimicrobials to be used in animal production. (Further information is available from: www.who.int/emc/diseases/zoo_global_principles).

The WHO criteria together with the current actions taken in Denmark are shown below.

A) Use of antimicrobial growth promoters that belong to classes of antimicrobial agents used in humans and animals should be terminated or rapidly phased out:

Antibiotic growth promoters have not been used in pig production in Denmark since 31 December 1999.

B) Data generated from the surveillance of antimicrobial resistance and antimicrobial usage should play a key role in the development of national policies for the containment of antimicrobial resistance;

The results of monitoring antibiotic resistance (see C) are used in developing the national policies for controlling antibiotic resistance (Veterinarian Antibiotic Policy available from www.svs.dk).

C) Programmes to monitor antimicrobial resistance in animal pathogens, zoonotic agents (for example, *Salmonella spp.* and *Campylobacter spp.*) and bacteria known to be indicators of antimicrobial resistance (for example, *E.coli* and *E. faecium*) should be implemented on bacteria from animals, food of animal origin and humans;

The DANMAP programme was started in 1995. A comparison is made of the occurrence of resistance in bacteria from food animals, food of animal origin and humans. Resistance is also monitored in commensal bacteria from food animals: *E. Coli, Enterococcus faecalis* and *Enterococcus faecium*. Results for these organisms show that marked changes in consumption of antibiotic growth promoters are reflected in the incidence of antibiotic resistance.

D) Relevant authorities should establish systems to determine the amounts of antimicrobials given to food animals;

Data on the amounts of antibiotics used in animal production have been available for some years, however the establishment of VetStat (see Section 6.2) will provide much more detailed information that can be used to reduce usage even further.

E) Information on the amounts of antimicrobials given to food animals should be made publicly available at regular intervals, be compared to data from surveillance programmes on antimicrobial resistance and be structured to permit further epidemiological analyses;

All the information on antimicrobial resistance and usage of antibiotics in animal production is published annually in the DANMAP report. (This is readily available and can be downloaded from the website at www.svs.dk).

F) Veterinarians should prescribe antimicrobials only for animals under their direct care;

Antimicrobials can normally only be prescribed by a veterinarian who is responsible for the healthcare of the animals.

G) It is the responsibility of the producers to ensure that production systems promote animal health and welfare. Antimicrobial usage, if necessary, should always be part of, not a replacement for, an integrated animal health programme. Such a programme is likely to involve hygiene and disinfection procedures, bio-security measures, management alterations, changes in stocking rate, vaccination and other relevant components;

A health advisory agreement is mandatory for all herds using medicines. The veterinarian is required to visit the production unit at least once every 35 days. The purpose of this is to develop a health plan for the herd and ensure it is kept up-to-date.

H) Veterinarians together with producers should be jointly responsible for the health of animals on the farm. Veterinarians and producers should agree policies and protocols for preventative strategies, health and treatment programmes and veterinary involvement in ongoing animal health management. These policies and protocols should comply with prudent use principles, good farming practice and quality assurance programmes;

A health advisory agreement is mandatory for all herds using medicines. The veterinarian is required to visit the production unit at least once every 35 days. The purpose of this is to develop a health plan for the herd and ensure it is kept up-to-date.

I) Use of antimicrobials for prevention of disease can only be justified where it can be shown that a particular disease is present on the premises or is likely to occur. The routine prophylactic use of antimicrobials should never be a substitute for good animal health management;

Treatment of animals is allowed only when there are clinical signs of disease or where animals might be expected to be in the incubation phase of a well-defined disease. The effect of this has been to restrict the extent of prophylactic use of antimicrobials.

J) Prophylactic use of antimicrobials in control programmes should be regularly assessed for effectiveness and whether use can be reduced or stopped.

The guidelines for prudent use of antimicrobials issued by the Danish Veterinary Laboratory stress that prudent use pre-supposes continuous evaluation of route of administration and dosage.

8.0 CONCLUSION

It is evident from this analysis that Denmark is already implementing all of the WHO Guidelines. In view of the size of the Danish pig industry, this represents a significant achievement and undoubtedly serves as a model for many other countries.

SUPPORTING INFORMATION

9.0 ZOONOSES IN THE UNITED KINGDOM

Concern about zoonotic infections in Great Britain has been heightened in recent years, particularly since the *E.Coli* 0157 outbreak in Scotland in 1996. This led to the funding of a number of new research projects. During 2000, two conferences were organised on behalf of DEFRA, Scottish Executive Rural Affairs Department, National Assembly for Wales, Department of Health and the Food Standards Agency. The object was to disseminate the results of current research and surveillance programmes, linking livestock with public health.

The 2000 Zoonoses Report was released in early 2002. It has been produced by a group representing the following organisations, under the Chairmanship of Dr Sarah O'Brien:

- Department for Environment, Food and Rural Affairs
- Department of Health
- Scottish Centre for Infection & Environmental Health
- Veterinary Laboratories Agency
- Scottish Agricultural College
- Public Health Laboratory Service, Communicable Diseases Surveillance Centre
- Department of Agriculture and Rural Development, Northern Ireland
- Department of Health and Social Services and Public Safety (Northern Ireland)
- Communicable Disease Surveillance Centre (Northern Ireland)
- Scottish Executive Rural Affairs Department
- National Assembly for Wales Agricultural Department
- Food Standards Agency
- Communicable Disease Surveillance Centre, Wales
- Public Health Laboratory Service, Laboratory of Enteric Pathogens

The report aims to provide information on zoonotic diseases and gives an insight into their prevalence and importance. With regard to monitoring and surveillance, the report states that:

> "...Control policies have been introduced to reduce the prevalence of pathogens in the food-chain and other areas. These include the implementation of legislation relating to the production of potable water and food production. The UK government operates a national microbiological food surveillance programme and carries out regular surveillance studies on foods and food processes. Local Authorities also carry out surveillance, although data from this activity are not collated nationally.

The Epidemiology of Foodborne Infections Group brings together surveillance data in humans and animals. There is a co-ordinating group on surveillance of animal disease and infection chaired by the Chief Veterinary Officer. In 1999 the National Zoonoses Group for England was set up to provide a high-level forum for discussions on zoonoses in England. The Group was established jointly by the Department of Health and MAFF (now DEFRA). It brings together the professionals from both central and local government involved in animal and public health aspects of zoonoses and their control in England. Similar Groups already exist in Scotland and Wales. The Group advises Agriculture and Health Ministers on zoonoses issues.

The Food Standards Agency (FSA) was set up on 1 April 2000. The Agency, which operates on a UK basis, was created by the government to protect public health from risks which may arise in connection with the consumption of food and otherwise to protect the interests of consumers in relation to food. The FSA also took over certain of the previous responsibilities of MAFF and the Department of Health in relation to food safety. In July 2000, the FSA announced a target to reduce foodborne disease by 20% by April 2006.

A full copy of this report and the first and second reports ~ Zoonoses Report UK 1998 and Zoonoses Report 1999 ~ are available on http://defraweb/animalh/diseases/zoonoses/reports.htm

9.0.1 Salmonella

A survey reported in December 2000, conducted by Dr Rob Davies[3] of the Veterinary Laboratory Agency, found *Salmonella* in the caeca of 23.0% and on the carcases of 5.3% of 250 pigs surveyed at slaughter during 1999/2000. 21.9% of the *S. typhimurium* isolated from caeca were phage type DT104. Most *S. typhimurium* isolates were resistant to tetracycline and sulphonamides; 20.2% of isolates were resistant to 6 antimicrobials.

Monitoring of the antimicrobial resistance in *Salmonella* isolated from animals and their environment in England and Wales has been done by the Veterinary Laboratories Agency since the early 1970s.

A recent paper published in the Veterinary Record has shown that in pigs the proportion of *Salmonella typhimurium* isolates, which were sensitive to all antimicrobials, fell from 23% in 1988 to 1.9% in 1999. The values for the *Salmonella* (excluding *S. typhimurium* and *S. Dublin*) were 53% in 1988 falling to 29.9% in 1999.[4]

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[3] Davies, R (2000) MAFF Conference (London) *Zoonotic Infections in Livestock and The Risk to Public Health*

[4] Jones Y.E., Chappell S, M°Laren I.M., Davies R.H. and Wray S (2002) *Veterinary Record*: 21, May 215, pp 649-654.

UK farmers are controlling *Salmonella* infection using the hazard analysis critical control point (HACCP) approach. The main source of infection is thought to be infected pigs in the grower and finisher accommodation. The UK is moving towards the "all-in, all-out" approach, which the Danes use, to act as a control against infection.

The UK "Code of Practice for the Prevention and Control of *Salmonella* in Pig Farms" was published in December 2000. It aims to provide guidance to pig farmers on:

- Best practice to minimize the risk of *Salmonella* entering the farm;
- Controls to prevent further spread of infection within the herd and to other farms;
- The cleaning and disinfection of the farm.

This is a voluntary code of practice although certain aspects such as the movement of pigs must comply with legislation.

These are just a few of the control measures now in place in the UK, most of which have been used by the Danes in their *Salmonella* Control Scheme for many years.

In the UK there are mixed views on the introduction of a similar surveillance scheme. Although catering and retail sectors, plus producer groups, are in favour of such a scheme, there are concerns regarding the costs of putting such a scheme in place. How would costs be met? Who would co-ordinate and control the scheme?

Trade implications for the UK pig industry may arise. In order to enhance the reputation of British pork, a unified approach is needed in order to generate nationwide data that can be used as part of a control scheme[5].

9.0.2 ZAP Salmonella

This is a zoonoses action plan for the British pig industry which has been developed by the British Pig Executive (BPEX).

The objective of this programme is to identify those farms where high proportions of pigs test positive for *Salmonella* antibodies, so that farms which are exposed to high levels of *Salmonella* can be pinpointed. As a result, producers will be able to take action to control the level of exposure.

ZAP Salmonella is an abattoir-based monitoring programme operated through farm and abattoir assurance schemes. Samples will be collected from 2% of pigs slaughtered at British Quality Assured Pig abattoirs. These samples will

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[5] Thompson, J.R et al (1999) *The Pig Journal:* 44 pp 105-116

then be analysed at a central laboratory using the Meat Juice ELISA test which was developed in Denmark and forms the basis of the Danish Salmonella control programme. Sampling will start in June 2002. As in Denmark, producers will be allocated to one of three categories by July 2003. The basis for allocation to these categories will be determined and reviewed continuously by the ZAP Salmonella monitoring programme management steering group. In order to concentrate resources on the worst affected farms, the following may be the basis of the initial allocation to ZAP categories:

ZAP 3 : the top 1% with the highest prevalence of *Salmonella* antibodies

ZAP 2 : the next 5% highest prevalence of *Salmonella* antibodies

ZAP 1 : all the other farms.

It is proposed that by June 2004 the scheme will be fully incorporated into the Quality Standard Mark. ZAP1 and 2 levels will be acceptable within the scheme. If a producer remains consistently in ZAP 3, the meat from the pigs may no longer be eligible to carry the QSM until an improvement can be demonstrated. Sanctions, including price adjustments, may be introduced.

ZAP 2 and 3 producers will be provided with an on-farm Salmonella control advice pack. ZAP 3 producers will be required to develop an action plan. This will be reviewed by the farm's own veterinary surgeon. Producers will be advised to use an approved consultant to review and advise on Salmonella control plans, and to help ensure that improvements are being achieved.

It is intended that producers will not be charged for monitoring during the first 3 years. Participating abattoirs have agreed to fund the cost of collecting the samples. The Food Standards Agency has agreed to provide financial support for the introduction of the scheme. DEFRA will provide assistance with the development of on-farm control strategies.

9.0.3 DT104

There is growing concern about the identification of an increasing proportion of DT104 with additional resistance to the first generation quinolone nalidixic acid in isolation from food-producing animals. Similarly, there have been reports of decreased susceptibility to the fluoroquinolone antimicrobial ciprofloxacin in isolations of DT104 from human beings. The emergence of decreased susceptibility to ciprofloxacin in DT104 is subsequent to the licensing in the UK, in November 1993, of the related fluoroquinolone enrofloxacin for use in food-producing animals. There is considerable controversy over the apparent association between enrofloxacin usage in food animals and the emergence of strains with decreased susceptibility to ciprofloxacin in human beings. An investigation into an outbreak caused by multi-resistant *Salmonella typhimurium* DT104 found that the clonal identity of the strains in cattle, a milk filter and the infected humans was the same in all 3 samples. In the US, the authorities are now convinced that the use of

enrofloxacin in animal production contributes to the development of antibiotic resistance in human pathogens[6].

Animal feed

To reduce the risk of *Salmonella* contamination in animal feed, *Salmonella* is monitored and controlled during the production process. Statutory monitoring for the presence of *Salmonella* in processed animal protein to be used in animal feeding stuffs is also done. DEFRA has issued codes of practice for the control of *Salmonella* in the production of animal feeds. These have been widely adopted. These include testing for *Salmonella* at various critical control points to facilitate risk assessment and enable corrective action to be taken.

In 2000 over 50,000 samples were tested by the industry. *S.enteritidis* and *S.typhimurium* are rarely reported in feeding stuffs and ingredients. *S.enteritidis* was not isolated in 1999 or 2000. *S.typhimurium* was isolated in 10 occasions in 2000 (7 in 1999). (ZOONOSIS Report, 2000)

9.0.4 VTEC 0157

G.A. Paiba et al conducted abattoir studies to investigate the faecal carriage of VTEC 0157 in animals sent for slaughter. Although the organism was present in the faeces of 4.7% of cattle slaughtered in GB, the value for pigs was only 0.3% (MAFF Conference, London, 2000).

9.0.5 Recent Developments

In a paper published by the Veterinary Record on September 2000, workers from the PHLS and VLA reported a large community outbreak, which involved 86 cases of *Salmonella typhimurium* DT104. Epidemiological investigation showed that 79% of cases had consumed milk from a local dairy which received raw milk supplied by two farms. DT104 was isolated from the milk filter and the cause of the outbreak was thought to be failure of in-farm pasteurization. Further work established that the same gene mutation was present in isolates from the dairy cattle, a milk filter and the infected humans. The same gene mutation was also identified in DT104 isolated from dairy cattle on one of the farms 4 months prior to the outbreak.

This evidence is entirely consistent with the hypothesis that the emergence of strains with decreased susceptibility to ciprofloxacin in humans is caused by resistance in DT104 in response to the use of enrofloxacin in food-producing animals. It is also relevant that other fluoroquinolones e.g. marbofloxacin and danofloxacin are used in animals.

[6] Walker R.A. *et al* (2000) *Veterinary Record* 147, 14, 395-396

9.0.6 Antimicrobial Sensitivity Report

The Antimicrobial Sensitivity Report (1999) summarises data on antimicrobial resistance data collated by the Veterinary Laboratory Agency (VLA) in the years 1998 and 1999 under the Food Safety and Zoonosis Programme. This is the first report of its kind to be published. It includes data on *Salmonella* and other organisms isolated at a network of 14 diagnostic veterinary laboratories in England and Wales.

The recording system was set up in 1998, so it is too early to determine any trends, however the base-line data will enable future trends to be assessed and it will be possible to monitor the effects of any interventions. In addition to the surveillance of veterinary clinical isolates, surveillance of sheep, cattle and pigs at slaughter was performed in 1999 and 2000.

The results for 1999 and 2000 have been prepared and collated by Dr Rob Davies and colleagues (see: Proceedings of Conference "*Surveillance for Antimicrobial Resistance in Domestic Livestock and the Risk to Public Health*") held at Stoneleigh, Warwickshire, February 2002 and organised by DEFRA.

A high level of resistance was found in *Salmonella* isolates from pigs to certain antimicrobials, in particular tetracyclines, sulphonamides and macrolides. There was a generally higher level of resistance occurring in bacterial organisms of porcine origin when compared with other domestic species.

98.8% of Enterococcus isolates from pigs at slaughter were resistant to tetracyclines. 89.9% were resistant to tylosin, with many isolates resistant to both.

The majority of both *C.coli* and *C.jejuni* isolates from pigs were resistant to tetracyclines (79% and 70% respectively). This finding is unlikely to have implications for human health because the predominant Campylobacter species in man is not the same as in pigs.

9.1 E.U.

In August 2001, the European Commission adopted proposals to review current legislation and to improve the prevention and control of zoonoses. New legislation is proposed with the object of reducing the occurrence of these organisms by setting community-wide targets for zoonotic agents in specific animal populations.

10.0 ANTIBIOTICS IN ANIMAL PRODUCTION

Historical Background

Antibiotics have been responsible for enormous improvements in public health due to their ability to control pathogens. Despite the progress made in the developed countries, world-wide infectious diseases still account for 25% of deaths and 45% in low-income countries. As we increasingly recognise the role of infectious agents and other diseases, even greater importance will be placed on treating and preventing infections. Anti-infective drugs are critically important in reducing the global burden of diseases[7].

There is widespread concern, however, that the growing incidence of antibiotic resistance, particularly in bacteria, is seriously limiting the effectiveness of many antibiotics.

If we are unable to replace antibiotics as they lose their effectiveness ~ and to limit the emergence and spread of resistance ~ some diseases may become untreatable, as they were before the discovery of antibiotics.

The recent outbreaks of Foot and Mouth Disease in animals serve as a timely reminder to what could happen in humans when a pathogenic infection gets out of control.

In the past, there has been a marked reluctance to tackle this issue decisively in both animal production and in medicine. In recent years there have been a number of initiatives which indicate that the issue is now being taken seriously.

11.0 ANTIBIOTIC RESISTANCE

Antibiotics have been used as growth promoters in animal feeding for several decades. In the late 1940's, the addition of antibiotics to feedstuffs became common practice in the animal industry. The animals were routinely given low doses of antibiotics as feed or water additives.

11.1 The Impact of Antibiotic Growth Promoters on Farming

During the period from 1950-1970 farming evolved rapidly into factory or intensive farming systems. The main driving forces behind this intensification of the farming industry were economic, as the mechanisation of agriculture facilitated the bulk movement of feedstuffs and manure and subsidies opened up opportunities for capital investment in buildings and equipment. This in turn increased profitability of livestock production. Concurrently, the average income of the consumer was increasing, leading to a demand for high protein foods. The development of antibiotics and vaccines enabled the farmer to control animal disease. This encouraged high density stocking, which previously would have caused loss of stock through death and disease.

[7] WHO: (7 September 1999) Anti-infective Drug Resistance: http://www.who.int/emc/amr.html

In pig and poultry units, prescription of antimicrobial drugs became routine to control enzootic diseases caused by exposure to high density stocking. As the incorporation of antibiotics in feeding stuffs became established as every day practice, pigs and poultry consuming these medicated feedstuffs invariably showed improved food conversion efficiency even in conditions where the animals were not exposed to infection. This led to research to develop the new category of antibiotic growth promoters or Zootechnical Feed Additives (ZFA). This type of additive is classified as a substance which is not itself a nutrient but is intended to enhance performance by improving the digestion and function of nutrients.

Antibiotics are extensively used in animal production in a number of different ways, namely:

- therapy: the treatment of disorders or disease;

- prophylaxis: the administration of antibiotics in advance of symptomatic disease;

- metaphylaxis: the use of antibiotics for the prevention of disease or the control of its spread. In the context of farmed livestock, when an animal which is kept, as part of a group, in close proximity to others contracts an infection, there is a high probability that others in the group will also be infected, whether or not they are exhibiting symptoms at that time. The administration of antibiotics to all animals in contact within the group, to treat asymptomatic disease in some and to prevent disease in others, is what we regard as metaphylaxis;

- growth promoters: antimicrobials used in low concentrations to stimulate an animal's growth, resulting in increased daily liveweight gain and feed conversion efficiency. The mode of action of growth promoters is thought to be associated with their effect on the composition and distribution of the intestinal microflora[8].

Note ~ The distinction between the different uses of antibiotics is not always crystal-clear, for example, tylosin (one of the 4 antibiotic growth promoters banned in the EU in 1999) was used both prophylactically and as a growth promoter.

Other areas where distinctions may be unclear are where antibiotics are prescribed for:

a) All pigs in a group, where only some pigs are observed to be sick.
   This blurs the distinction between therapy and metaphylaxis.

Or,

[8] Advisory Committee on the Microbiological Safety of Food (1999) *Report on Microbial Resistance in Relation to Food Safety*; London, The Stationery Office

b) All pigs in a group are routinely treated to prevent sickness.
This also blurs the distinction between prophylaxis and growth promotion, as the drug may be administered by topping up feed to preserve normal rates of growth in poor housing conditions, that are likely to predispose the animal to enzootic pneumonia.

12.0 CONCERNS ABOUT THE USE OF ANTIBIOTICS

In Great Britain, the Swann Committee examined the use of antibiotics in animal husbandry and veterinary medicine in the 1960s. The report, issued in November 1969, concluded that "the administration of antibiotics to farm livestock, particularly at sub-therapeutic levels, poses certain hazards to human and animal health". It was particularly concerned about the development of enteric bacteria of animal origin and by the fact that this resistance was transmissible to other bacteria. The report recommended that antibiotics should be excluded from animal feed:

- unless specifically prescribed for this purpose by a vet;
- if they are used as therapeutic agents in human or veterinary medicine; or,
- if they are associated with the development of cross-resistance to drugs used in humans.

The relevance of these recommendations is widely accepted, however they are rarely implemented in full.

This was followed by the Lamming Report in 1992, which highlighted a number of concerns about the use of antibiotics in animal feedstuffs. The main points being:

- the lack of farmers' understanding, which could lead to a misuse of veterinary medicines;
- to recommend the monitoring of resistance because of concern about *Salmonella* and *E. coli*;
- to reinforce the recommendation of the Swann report that antibiotics which could give cross-resistance to those used in human medicine should not be used as growth promoters;
- similar precautions should apply to antibiotics used in any prophylactic treatment.

Although the recommendations in the Swann report are often considered to be the benchmark, they have been criticised. The Standing Medical Advisory Committee (SMAC) in the UK, which reported before the House of Lords Committee, noted that the Swann Committee did not recommend restrictions

on the veterinary use of antibiotics belonging to chemical families also used in man.

At about the same time, the House of Lords Select Committee on Science and Technology was working on a detailed report entitled, "Resistance to Antibiotics and Other Antimicrobial Agents"[9]. In preparing the report, the Committee considered evidence from a range of experts in the field. In the introduction, the report comments:

> " This enquiry has been an alarming experience, which leaves us convinced that resistance to antibiotics and other anti-infective agents constitutes a major threat to public health and ought to be recognised as such more widely than at present."

For the reader who wishes to acquire greater understanding of antibiotic resistance, this report is well worth consulting. Here are some extracts:

> "It is now known, for example, that genetic interchange can take place between a much more diverse variety of organisms than was formerly thought and is probably a common event in the natural world...
>
> There is a global pool of resistance genes which can spread between different bacterial populations occupying different habitats, e.g. between man, animals and the environment...
>
> ...it is indisputable that resistance has developed to many new agents after their introduction, with consequent diminution or actual loss of their former value to medicine. Thus has appeared the vicious circle repeatedly witnessed during the last half century, in which the value of each new antibiotic has been progressively eroded by resistance, leading to the introduction of a new and usually more expensive agent, only for this in its turn to suffer the same fate."

With respect to the use of growth promoters in animal production, the Committee concluded:

> " We specifically considered the use of antibiotic substances as growth promoters in food animals and their relevance to the problem of antibiotic resistance. In the past, growth promoters have been generally regarded as of no (or little) direct use in clinical medicine. However, they are able to give rise to antibiotic resistance, in some cases in a way which could impact the use of related substances in human medicine. It should also be kept in mind that clinical applications of related substances might be developed at some future date. The Committee fully supports

[9] House of Lords Select Committee on Science and Technology (1997-1998) London, The Stationery Office.

the recommendations of the Swann Committee. To comply with Swann, antibiotics which are used for the treatment of infections in humans and animals should not be used as growth promoters[10]."

The Committee concluded that:

- There is a continuing threat to human health from imprudent use of antibiotics in animals;

- Antibiotic growth promoters such as virginiamycin, which belong to classes of antimicrobial agent used (or proposed to be used) in man and are therefore most likely to contribute to resistance in human medicine, should be phased out, preferably by voluntary agreement between the professions and industries concerned, but by legislation if necessary;

- The veterinary profession must address the problem of over-use of fluoroquinolones and other potent agents of importance to human medicine by introducing rapidly a Code of Practice detailing when and how such compounds should be prescribed.

It also recommended that:

- DEFRA and the Food Standards Agency should consider the need to improve surveillance of resistance patterns in animals;

- Departmental and Agency boundaries must not be allowed to prevent the Government from getting a grip on the whole of the issue of resistance, in the interests of public health. A single multi-disciplinary Government committee to oversee all aspects of antibiotic use, as recommended by the Swann report, should now be established.

In the U.K. the Soil Association has been actively campaigning for action to be taken to deal with antibiotic resistance. In 1998 and 1999 the Association produced a two-part report "The Use and Misuse of Antibiotics in UK Agriculture". This was followed by Part 3 in 2001.[11 12 13]

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[10] Advisory Committee on the Microbiological Safety of Food (1999) *Report on Microbial Resistance in Relation to Food Safety*; London, The Stationery Office

[11] Harvey, J. & Mason, L. (December) *The Use and Misuse of Antibiotics in UK Agriculture Part 1: Current Usage*; The Soil Association.

[12] Young, R. *et al,* (August 1999) *The Use and Misuse of Antibiotics in UK Agriculture Part 2: Antibiotic Resistance and Human Health*; The Soil Association.

[13] Young, R. *et al,* (June 2001) *The Use and Misuse of Antibiotics in UK Agriculture Part 3: Too Hard to Swallow: the truth about drugs and poultry*; The Soil Association.

13.0 INTERNATIONAL CONCERNS

13.1 World Health Organisation

In the Spring of 1999, Linda Tollefson comments as follows when speaking at the WHO meeting in Geneva:

> " The global emergence of resistance to antimicrobics has compromised control of many bacterial pathogens. Foodborne pathogens such as *Salmonella* are rarely transferred from person to person in industrialised countries. Therefore, human use of antimicrobials is unlikely to be a significant contributor to the development of antimicrobial resistance, which suggests that the most probable source of most resistance is use of antimicrobials in other sources such as food producing animals. Increases in quinolone-resistant Salmonella and Campylobacter isolates have been reported since the licensing of fluoroquinolones for use in animals in the Netherlands, the UK, Spain and the U.S. Additionally multiple resistance has emerged among many bacterial strains including *Salmonella* species.[14] "

In September 1999, a WHO paper on 'Anti-infective drug resistance' stated that:

> " The effectiveness of these drugs is diminishing as drug-resistant microbes develop and spread. We need to define more clearly the magnitude of the resistance problem and the global impact it has on mortality, morbidity and health care costs. To better understand the situation and to provide an early warning of new resistant strains, surveillance of resistant infections is critical. We will only slow down the emergence and spread of resistance by more careful use of anti-infective drugs, both in human medicine and in areas of non-human use. Successful containment of resistance will require the collaboration of many different groups.[15] "

Several studies have implicated the use of avoparcin as a selective pressure. The use of avoparcin as a feed additive has been suspended. In an article relating to the Vancomycin-Resistant Enterococci (VRE), McDonald & Jarvis noted that the bacteria were reported in an increasing number of countries and that, during 1996, VRE were reported for the first time from Sweden and Australia, while the first hospital outbreaks had occurred in Germany, Italy and Canada. In the U.S. surveillance system hospitals, the percentage resistant to

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[14] Tollefson, L. *et al*, WHO Geneva, 31 March – 1 April 1999, *Informal Information Meeting on Antimicrobial Resistance Surveillance in Foodborne Pathogens*; 6 December 1999. http:/www.who.int/emc/disease/zoo/meetings/AMRfoodmeeting.html

[15] WHO, 7 September (1999) *Anti-infective Drug Resistance*, (http:/www.who.int/emc/amr.html, 6 Decemebr 1999)

vancomycin increased in intensive care unit patients from 0.4% in 1989 to 10.8% in 1995, whereas the percentage from non-intensive care unit patients increased from 0.3% in 1989 to 10.4% in 1995[16].

In September 2001, the Director-General of the WHO, Dr Gro Harlem Brundtland announced the Global Strategy, which is designed to control the spread of drug resistance. Currently, 50% of all antibiotic production is used in agriculture for the treatment of sick animals and as growth promoters. The Global Strategy recommends a series of actions, which include mandatory prescriptions for all antibiotic use for disease control in animals and the phasing out of antibiotics as growth promoters.

13.2 U.S.A.

13.2.1 Alliance for the Prudent Use of Antibiotics (APUA)

The Alliance for the Prudent use of Antibiotics (APUA) is a non-profit making, international organization solely dedicated to preserving the power of antibiotics. It conducts educational, research and international networking activities to promote the appropriate use of antibiotics around the world. It has recently published a report entitled "The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences".

Having reviewed the scientific evidence the following conclusions were reached:

- All uses of antimicrobials in animals, agriculture and humans contribute to the global pool of antimicrobial resistance genes in the environment.

- Antimicrobial resistance in pathogenic bacteria limits treatment options, raises health care costs and increases the number, severity and duration of infections.
- Commensal bacteria also contribute to the antimicrobial resistance problem by serving as reservoirs of resistance genes transferable to pathogenic bacteria.

- It is estimated that, in the United States, the amount of antimicrobials administered to animals is comparable to that used in humans. In contrast to use in humans, much of the antimicrobial use in food animals consists of administration to large groups for non-therapeutic applications, such as growth promotion and disease prevention.

- Antimicrobial use in food animal production selects for resistant strains and amplifies their persistence and dissemination in the environment.

- Transfer of bacteria from food animals to humans is a common occurrence.

[16] McDonald & Jarvis, (1997) Curr. Opin. Infect. Dis 10: 304-9; House of Lords Select Committee on Science and Technology, 1997-98, *Resistance to Antibiotics and other Antimicrobial Agents Report*; London, The Stationery Office

- Use of antimicrobials in food animals contributes to the growing problem of antimicrobial resistance in animal and human infections.

The following policy recommendations were made:

1. Antimicrobial agents should not be used in agriculture in the absence of disease.

2. Antimicrobials should be administered to animals only when prescribed by a Veterinarian.

3. Quantitative data on antimicrobial use in agriculture should be made available to inform public policy.

4. The ecology of antimicrobial resistance should be considered by regulatory agencies in assessing the human health risk associated with antimicrobial use in agriculture.

5. Surveillance programmes for antimicrobial resistance should be improved and expanded.

6. The ecology of antimicrobial resistance in agriculture should be a research priority.

13.2.2. Union of Concerned Scientists

The Union of Concerned Scientists (UCS) estimates that 24.6 million pounds (11,181 tonnes) for all non-therapeutic use of antimicrobials in cattle, pigs and poultry is much higher than the value reported by the Animal Health Institute in 2000. This is 8091 tonnes, of which 1409 tonnes were attributed to growth promotion and the remainder for therapeutic use and disease prevention in all animals. It should be noted this value is based on the assumption that the total antimicrobial production is 22,727 tonnes, of which 35% is for use in animals. The most credible estimate was produced by the Institute of Medicine for 1985 which was 7,318 tonnes for sub-therapeutic use in cattle, pigs and poultry. If the Animal Health Institute value is accurate, it would mean that total usage in animals has remained about the same, despite a big increase in the numbers of animals being produced. [17] [18]

The Union of Concerned Scientists (UCS) in the USA has concluded that the surveillance programmes to determine usage of antimicrobials in the livestock and food systems are rudimentary. This means that the most basic data on the amounts of antimicrobials used in cattle, pigs and poultry and how the

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[17] Animal Health Institute, 2000. "*Survey indicates most antibiotics used in animals are used for treating and preventing disease*". Press Release. February 14.

[18] Institute of Medicine. 1989. *Human Health Risks with Sub-therapetic Use of Penicillin or Tetracyclines in Animal Feed*. Washington D.C.: National Academy Press.

patterns of use have changed over time are not available to the public, the public health community, or the regulators. Consequently the UCS has conducted a detailed study to estimate the usage of antimicrobials in the US cattle, pig and poultry industries, which was published as a report entitled "Hogging It ~ Estimates of Antimicrobial Abuse in Livestock". [19]

While it has been necessary to make assumptions and judgements, nevertheless the UCS has produced relevant information. The difficulties of obtaining reliable data are illustrated by the fact that the state of South Dakota does not require any information to be reported on the usage of antibiotics in livestock. The FDA, however, is committed to establishing a data-gathering system to get some indication of the amount of antibiotics utilised in livestock production.

The UCS estimate for non-therapeutic purposes in pigs was 4694 tonnes in 1998, which works out at about 50g per pig. There are about 5 times as many pigs slaughtered in the US than in Denmark. This compares with 57.3 tonnes used in Denmark for treatment of all animals and 49.2 tonnes for growth promoter usage in 1998. With the phasing out of growth promoters, the latter figure has been reduced to zero. Even if the UCS value is inflated, it is clear that the usage in the USA is much higher than it is in Denmark.

13.3 Australia

In Australia the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) report "The use of antibiotics in food-producing animals and humans" was published in October 1999. Having assessed the scientific evidence for the link between the use of antibiotics in food producing animals and the emergence of antibiotic-resistant bacteria and their spread to humans, the Committee made a series of recommendations for appropriate future management of antibiotic use.

- the emergence of resistant bacteria in humans and animals following antibiotic use;
- the spread of resistant animal bacteria to humans;
- the transfer of antibiotic-resistance genes from animal bacteria to human pathogens;
- resistant strains of animal bacteria causing human disease.

The main recommendation, which has been accepted by the Government, is:

[19] UCS Report : (2001) Hogging It: *Estimates of Antimicrobial Abuse in Livestock*: Mellon, M, Benbrook, C, and Lutz, K: Union of Concerned Scientists.

"That Australia adopt a conservative approach to minimise the use of antibiotics in humans and animals and, to further this policy, that infeed antibiotics used in food-producing animals for growth promotant purposes, or other routine uses where duration and dose level are the same, or very similar, should not be used unless they:

- are of demonstrable efficacy in livestock production under Australian farming conditions; and

- are rarely or never used as systemic therapeutic agents in humans or animals, or are not considered critical therapy for human use; and

- are not likely to impair the efficacy of any other prescribed therapeutic antibiotic or antibiotics for animal or human infections through the development of resistant strains of organisms."

More specifically, the National Registration Authority was charged with conducting reviews of the use of antibiotic growth promoters currently registered in Australia, which do not appear to fulfil the criteria listed in the above recommendation.

This has been reinforced by the Government. At the time the Government response was published (August 2000) the position was as follows:

- the Avoparcin review, which was nearing completion, is suspended as both of the registrants withdrew the product from the market. Registration and approval ceased on 30 June 2000;

- a review of Virginiamycin commenced during the second half of 2000, and was due to be completed by December 2001; and

- A review of the macrolides will commence in the first half of 2002, and will be completed by June 2003.

The Australians have been keen to learn from the experience gained in developing DANMAP in formulating their own national strategy.

13.4 Canada

The Advisory Committee of the Canadian Veterinary Drug Directorate has prepared a report entitled "Uses of Antimicrobials in Food Animals in Canada: Impact on Resistance and Human Health" which was released in June 2002.

The Committee recognised that food animals are important sources of many bacterial infections in humans. In Canada, the main pathogens are *Salmonella enterica* and *Campylobacter jejuni*. Many, but not all, of the human infections which originate in animals are resistant to antimicrobials. Antimicrobial use in animals is probably the major factor contributing to the resistance. The resistance may increase the burden of human illness directly because:

- Resistant zoonotic infections are more difficult or expensive to treat than susceptible infections.

- Some resistant pathogens may be more virulent or pathogenic to humans than susceptible pathogens so causing more severe or longer-lasting disease.

- The presence of antimicrobial resistance in zoonotic pathogens can increase the number of cases of illness, because prior antimicrobial therapy can increase the risk of disease.

The Committee specifically identified concerns about the use of fluoroquinolones in animals which can select for resistance (or reduce susceptibility) in human pathogens, especially *Campylobacter jejuni* and *Salmonella enterica*. There are also concerns about multiple resistance as, for example, in *Salmonella Typhimurium* DT104.

The Committee expressed a number of concerns about the regulation and sale of antimicrobials in Canada for use by food-producing animals. These include:

- The lack of specific plans to manage risk associated with antimicrobial resistance transmitted from food animals.

- The lack of credible, scientifically valid methods and criteria to assess the safety of veterinary drugs with respect to antimicrobial resistance and human health.

- The OTC sale of antimicrobials for use in food animals.

- The fact that some veterinarians obtain a portion of their income from the sale of antimicrobial drugs they prescribe is a conflict of interest with regard to prescription-only drugs.

- The lack of a clear and comprehensive policy on extra-label use, especially as it pertains to antimicrobial resistance,

- Farmers can legally import antimicrobials from retailers overseas for use in their own animals.

- Some active pharmaceutical ingredients are being illegally offered for sale and administered as drugs directly to food animals.

Points of concern specifically related to resistance included:

- Most of the classes of drug used in animals are also used in humans.

- Some of these are registered for use in feed as growth promoters or prophylactics.

- Some antimicrobials used in humans are administered routinely to large numbers of animals for treatment, prophylaxis or growth promoters.

- Modern production methods dictate that even therapeutic treatments in some types of animals necessarily involve treatment of entire groups of animals through feed or water, thereby increasing the potential exposure to resistance selection pressures.

- Some drugs are registered for two or more of the following categories: growth promoters/improved feed efficiency, disease control prophylaxis or therapy.

In Canada, data on the quantities of various antimicrobials used in animals is not collected in a way that helps to further the understanding of resistance and its impact on human health. There is also a lack of reliable data on resistance.

The Committee recommended changes in the ways that antimicrobials are regulated, distributed and used in animals. The experiences of countries such as Denmark and Sweden should be carefully analysed to see what lessons can be learned for developing new policies and strategies in Canada.

14.0 ACTION TO CONTROL ANTIBIOTIC RESISTANCE

14.1 United Kingdom

In December 1998, The Government Response to the House of Lords was published. This recognised that antimicrobial resistance is a major threat to public health and released the House of Lords report.

The Government strategy to deal with antimicrobial resistance is based on:

- surveillance ~ to provide the information base for action;

- prudent antimicrobial use ~ to limit unnecessary pressure for the emergence of resistance;

- infection control ~ to limit the spread of infection in general and thus some of the need for antimicrobial agents, and of antimicrobial resistant infection in particular.

A number of initiatives had been taken, which include the following:

- Progress by the Public Health Laboratory Service in developing a 5-year antimicrobial resistance surveillance programme;

- An investigation into microbial resistance in the food chain being conducted by a working group of the Advisory Committee on the Microbiological Safety of Food (ACMSF) was in progress. The Chairman had recommended that virginiamycin, spiramycin and tylosin phosphate should be phased out as growth promoters at the earliest opportunity because there is a medical equivalent antimicrobial in use;

- The Government had supported a European Commission proposal to ban the use of certain antimicrobial growth promoters in animals with effect from 30 June 1999.

The ACMSF report entitled. 'Microbial Antibiotic Resistance in relation to Food Safety' was published in August 1999 and examined issues which included:-

- the high prevalence of multiple-resistant strains of *Salmonella typhimurium* definitive phage type (DT) 104 and evidence of food-associated infection;

- concern about other resistant strains of *Salmonella*;

- reports of Campylobacters developing resistance as a consequence of quinolone usage in farming;

- the therapeutic and prophylactic use in animals of antibiotics of importance in treatment of human infections;
- EU consideration of the case for banning the use as growth promoters of a number of antibiotics;

- the different approach to the veterinary (as compared with the human clinical) use of antibiotics whereby drugs are administered to large groups of animals or poultry at the appearance of disease, on the premise that this is the most effective means of preventing the spread of disease within the group; and

- the possibility that imported foods might be more likely to contain antibiotic-resistant organisms than domestically produced food as a consequence of the freer availability of antibiotics to agricultural producers in other countries[20].

The Committee found that resistant bacteria in food animals have arisen as a consequence of the use of antibiotics in the farm environment and current husbandry practice. Furthermore, the Advisory Committee was convinced that, as a result, some of the resistant bacteria such as *Salmonella* and Campylobacter appear in both farm animals and humans. The Committee was satisfied that some resistant bacteria are transferred to humans via the food chain.

[20] Advisory Committee on the Microbiological Safety of Food (1999) *Report on Microbial Resistance in Relation to Food Safety*; London, The Stationery Office

There was particular concern about the quinolones (including the fluoroquinolones). These are invaluable agents for the treatment in humans of infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) and of enteric fevers caused by *Salmonella typhi* and *Salmonella paratyphi A, B* and *C*.

It was hoped that the quinolones, when first introduced, would make the development of resistance in bacteria, including Campylobacters, almost impossible. Unfortunately, this prediction proved to be over-optimistic. Campylobacters are the most commonly recognised foodborne pathogens in the UK. There is a belief that the emergence of quinolone-resistant Campylobacters reflects the use of drugs in veterinary medicine.

The Committee concluded that there must be a reduction in the exposure of farm animal bacterial populations to antibiotics. This could be achieved by the implementation of a strategy based on the following:

- constraining the use of growth promoters;
- paying much greater attention to the question of resistance in the approval procedures for veterinary medicines and in post-marketing surveillance;
- stimulation of the farming industry, its suppliers and the veterinary professions to develop strategies for reducing the use of antibiotics for therapy, prophylaxis etc. over time and confronting the difficulties caused by the veterinary use of fluoroquinolones;
- introducing tighter controls on medicated animal feeding stuffs; and
- improving our understanding of resistance in bacteria isolated from food animals and foodstuffs, of human infections associated with antibiotic-resistant foodborne pathogens and of ways in which the food chain contributes to human infections with antibiotic-resistant micro-organisms.

The Committee accepted that the danger of antibiotic-resistant micro-organisms can be reduced by raising standards of husbandry in the industry, and by closer focus of veterinarians and farmers on the threat of microbial antibiotic resistance.

During 2000, the Government responded positively to the recommendations of the Advisory Committee.

14.1.2 The SMAC Report

In July 1997, the Chief Medical Officer asked the Standing Medical Advisory Committee (SMAC) to examine the issue of antimicrobial resistance. As a consequence SMAC set up an interdisciplinary sub group, which produced a detailed report.

The key points were:

- 50% of antibiotic use in the UK is in man and 50% in animals
- in *S. typhimurium*, 80% of isolates received in 1996, were multi-resistant and most were phage type DT104. This strain is now established in poultry, sheep and pigs, and has been isolated from human foods. *S. typhimurium* is increasingly resistant to sulphonamides, trimethoprim and ciprofloxacin.

The report also included the following recommendations on the use of antibiotics, which have relevance to animal production:

- a strategic system should be developed as swiftly as possible for resistance surveillance of antimicrobial resistance.
- alternative means of animal husbandry be developed so that the use of antibiotics as growth promoters can be discontinued.

The use of antibiotics in veterinary practice is a major factor in promoting resistance among enteric pathogens and, perhaps, enterococci. It was noted that the Swann Committee did not recommend restrictions on the veterinary use of antibiotics belonging to chemical families also used in man. This emerged as a major concern when it was observed that enteric bacteria selected for resistance to the veterinary antibiotic apramycin were also resistant to its analogue, gentamicin, which is used for severe infections in man.

The report drew attention to the fact that the Veterinary Products Committee (VPC) had approved the use of enrofloxacin (a fluoroquinolone related to the human drug ciprofloxacin) in animals at the end of 1993. This was despite the concern about the rapid emergence of resistance in Campylobacters following enrofloxacin use in poultry flocks and despite information from the Netherlands that its use had contributed to the emergence of ciprofloxacin-resistant Campylobacters.

Furthermore even though some families of antibacterial agents are presently only used in animals, new analogues may be used in man. Thus dalfopristin/quinupristin (Synercid) and everninomycin (Ziracin), which are now under development as agents against MRSA and VRE, are analogues of virginiamycin and avilamycin, respectively, which have long been used as growth promoters.

14.1.3 The UK Action Plan

Since the SMAC Report, there have been reports from the House of Lords and the Committee on the Microbiological Safety of Food, as well as the Government response to it. The latest development has been publication of the Government's strategy clarified in June 2000. The document published by

the Department of Health is entitled, "UK Antimicrobial Resistance Strategy and Action Plan" (Department of Health, June 2000).

This document identifies:

- Surveillance: to monitor 'how we are doing', and provide the data on resistant organisms, illness due to them and antimicrobial usage necessary to inform action;

- Infection control: to reduce the spread of infection in general (and thus some of the need for antimicrobial agents) and of antimicrobial resistant micro-organisms in particular and;

- Prudent use of antimicrobials in humans and animals as 'key elements' in attempts to control antimicrobial resistance: to reduce the 'pressure for resistance' by reducing unnecessary and inappropriate exposure of micro-organisms to antimicrobial agents in clinical practice, veterinary practice, animal husbandry, agriculture and horticulture.

The report indicates how a coordinated approach to the problem is required and it forms a basis for action by Government departments and other organisations over the next 3 years. Some of the key players include: Ministry of Agriculture, Fisheries and Food (Now DEFRA); Food Standards Agency (FSA); Public Health Laboratory Service (PHLS); British Veterinary Association (BVA) and Responsible Use of Medicines in Animals Alliance (RUMA) (co-ordinated by the NFU).
The Interdepartmental Steering Group, chaired by Dr P Troop (DH Deputy Chief Medical Officer) and initially set up to co-ordinate the Government's response to the House of Lords Report, will oversee and co-ordinate work in this field. It will be advised by the newly established Expert Advisory Committee on Antimicrobial Resistance. (Chair: Professor Richard Wise)

The European Commission's Scientific Steering Committee will receive input from the UK, at EU level. The UK will also argue for the future framework for European action in the field of public health to make antimicrobial resistance a priority for action. The UK will press for antimicrobial resistance to be given priority, at international level, in the WHO's next global and biennial work programmes.

The Government's strategy comprises two main aims:

- to minimise the morbidity and mortality due to antimicrobial resistant infection;

- to maintain the effectiveness of antimicrobial agents in the treatment and prevention of microbial infections in man and animals.

In Scotland, the relevant local aspects have been incorporated into the UK Action Plan. (**www.scotland.gov.uk**)

Key Elements: Surveillance

The objective of this area is to ~

- ensure appropriate systems are established and maintained to monitor UK usage of antimicrobials in order to:

- support optimal prescribing policies and practice;

- relate UK data on patterns of use and antimicrobial resistance, as part of national and international efforts to improve knowledge on how use may lead to the build up of resistance.

- improve the correlation of data on patterns of antimicrobial use, antimicrobial resistant organisms, and illness due to them, in animals and man.

By taking account of user needs, the PHLS is to establish and develop a national antimicrobial resistance surveillance programme. The PHLS will also provide the lead for the UK input into the current EU and WHO drug resistance surveillance projects.

Collection and reporting of antimicrobial resistance data on foodborne pathogens at the point of harvesting will be improved by DEFRA. It will collate and publish information on other pathogens as well as *Salmonella*. A baseline survey of patterns of antimicrobial use as veterinary medicines and growth promoters will also be commissioned by DEFRA.

The UK will continue to press for priority to be given to antimicrobial resistance surveillance in the new EU communicable disease surveillance network.

DEFRA ACTION PLAN

This plan is being taken forward by the DEFRA Antimicrobial Resistance Co-orindation (DARC) Group. It is chaired by Dr Mike Rutter of the VMD. The terms of reference are:

"To co-ordinate and direct DEFRA activities on antimicrobial usage in animals and microbial antibiotic resistance in feeding stuffs, animals and food."

The remit is:

- To provide a DEFRA response to the ACMSF Report;

- To develop a DEFRA Action Plan and Strategy on antimicrobial resistance in animals;

- To monitor surveillance studies on antimicrobial usage and microbial resistance;

- To promote prudent and optimal use of antimicrobial products in animals;

- To investigate alternatives to the use of antimicrobial products in animals;

- To monitor research and development regarding antimicrobial resistance;

- To raise public awareness of the issue of antimicrobial resistance.

The current position on the action plan has been agreed.

1. It is essential to ensure that the methods used for collecting samples, testing and the criteria for interpreting the results are standardised across the UK so that data will be comparable and could also be compared to data from other EU countries (and even globally). Future monitoring of antimicrobial resistance will need to be co-ordinated across the EU in order to get comparable and useful data. In this regard, a bid will be submitted once obligations to the EU are clearer. EU support for this objective will be important, and discussions about the co-ordinated approach with European counterparts will be arranged when practical.
2. It will also be necessary to establish certain levels of quality assurance to ensure that all the elements of the surveillance are working to the same standards with regards to sampling methodologies as well as electronic gathering and reporting of data. It is also vital that the data generated will be comparable to data generated from similar schemes looking at human isolates.

3. The VLA and PHLS will be able to provide valuable expertise in this area as they have a great deal of experience in implementing large-scale surveillance programmes. The VLA and PHLS have set up a working group, to which SAC will be invited, to standardise methodologies. VLA plan to upgrade systems once standardised methodology has been agreed with PHLS although it is recognised that this may require additional funding of around £300K. The VLA will bid for these funds in their normal way. Additionally, input from the PHLS representative will be essential as there are already UK-wide surveillance schemes for human isolates which may well provide a framework to work to and, eventually, to feed in to. A summary of both the human and animal isolate databases will be provided on the web.

4. Surveillance programmes will need to be flexible in order to follow up on problems identified. The starting point and follow

up actions will be based on the Government's response to the ACMSF report but the strategy will need to be further developed to take into account priorities identified across Europe and globally.

Infection Control

The objectives of this area are solely concerned with the human field. They are to ~

- strengthen infection control practices and processes in hospitals and the community.
- promote collaboration between the Member States of the EU and the WHO European Region to this end.

Prudent Antimicrobial Use in Animals

The objective of this area is to:

- promote optimal antimicrobial prescribing in animals. This will be done through the VMD encouraging professional education and also encouraging the production and promulgation of guidelines/codes of practice for prescribing, including through BVA, NFU and NOAH.

- reduce unnecessary and inappropriate use of antimicrobials for non-therapeutic use in animals. The VMD will review appropriate usage, including as growth promoters, in light of advice from the Advisory Committee on the Microbiological Safety of Food (ACMSF) and the Veterinary Products Committee, and EU decisions.

- use the regulatory framework to improve optimal prescribing (in the UK and Europe) where appropriate. The VMD will critically assess existing products at the time of renewal of marketing authorizations and ensure that data sheets and product characteristics summaries are appropriate and consistent (with those for other products containing the antibacterial active ingredient). In the authorisation process for new antimicrobials, the VMD will require the development of optimised dosing rates and strategies based on recent advances in pharmacokinetic and pharmacodynamic data and, where necessary, require new dose rates and strategies for currently authorised antimicrobials.

A co-ordinated programme of research will be promoted which will include a specific area of alternative means of animal husbandry to allow discontinuation of antibiotics as growth promoters.

Information on the sales of antimicrobials is now available in the UK (see Tables 14.1.1 and 14.1.2)

Table 14.1.1: Sales of Antimicrobial Therapeutic Products and Growth Promoters 1993-2000
(tonnes active ingredient)

	1993	1994	1995	1996	1997	1998	1999	2000
Therapeutic antimicrobials	392	445	486	533	495	433	383	437
Antimicrobial growth promoters	83	88	122	96	69	89	28	24
Total antimicrobials ~ food animals	**475**	**533**	**608**	**629**	**564**	**522**	**411**	**461**

Veterinary Medicines Directorate: February 2001

Table 14.1.2: Break down of Antimicrobial Therapeutic Products 1998-2000
(tonnes active ingredient)

	1998	1999	2000
Tetracyclines	233	192	228
Trimethoprim/sulphonamides	80	82	94
β-lactams	60	52	49
Aminoglycosides	24	20	12
Macrolides	24	29	41
Fluoroquinolones	1	1	1
Others	11	7	11
TOTAL	**433**	**383**	**436**

Veterinary Medicines Directorate: February 2001

Table 14.1.3: Distribution of sales of therapeutic antimicrobials by food animal species 1998-2000
(tonnes active ingredient)

Species	**1998**	**1999**	**2000**
Cattle	11	11	10
Sheep	11	11	0.3
Pigs	90	89	96
Poultry	14	11	24
Fish (salmon, trout)	5	4	2
Multi-species	313	267	304
TOTAL	**433**	**383**	**436**

In the U.K. there were 12.7 million pigs produced in 2000. Taking the 96 tonnes of active ingredient from the above table would give a value of 7.6g per pig ~ 3.6g per pig in Denmark, however, a substantial proportion of multi-species antibiotics must also be used for pigs, although a break-down cannot be supplied. Even if only a third of this amount is used with pigs, this would

take the value per pig up to about 15g. In addition, there will be a contribution from the 24 tonnes of growth promoters used which would increase the value by about 2g per pig.

RUMA

In the UK, The Responsible Use of Medicines in Agriculture Alliance (RUMA) has been established. This is a coalition of organisations with agricultural, pharmaceutical and retail interests. The Pig Working Group of the Alliance has produced guidelines entitled, "Responsible use of antimicrobials in pig production" which has the following objectives:

- To review the use of antimicrobials in pig production, and to produce responsible use guidelines to farmers;
- To aim to establish and communicate practical strategies by which the need for the use of antimicrobials might be reduced;
- Ultimately to enable a livestock producer to discontinue unnecessary antimicrobial use without adversely affecting the welfare of the animals or the viability of the business.

Guidelines for farmers are included in the paper as follows:

- Regard therapeutic antimicrobial products as complementing good management, vaccination and farm hygiene;
- A herd health plan should be drawn up that outlines routine preventative treatments (e.g. biosecurity, vaccination and worming programmes etc);
- Initiate treatment with a medicine that is subject to a veterinary prescription only with formal veterinary approval;
- In the case of in-feed medication this will be provided by a Medicated Feeding Stuff (MFS) Prescription;
- Ensure that accurate information is given to the attending veterinary surgeon in order that the correct diagnosis, medication and dosage can be calculated for the animals concerned, and ensure that clear instructions for dosage and administration are obtained and passed on where necessary to the staff responsible;
- Ensure that a prescribing veterinary surgeon is aware of other medicines being administered, because adverse reactions sometimes occur;

- Always complete the course of treatment at the correct dosage. Ensure that the dosage is dispensed in an effective manner by careful administration;

- For in-feed or in-water medication ensure that the end of medication is accurately determined by cleaning the header tank or feed bins as appropriate;

- Ensure that the appropriate withdrawal period is complied with prior to slaughter of the treated animals or the sale of milk for human consumption. In general the withdrawal time required is specified on the Medicated Feeding Stuff Prescription in the case of in-feed antimicrobials, or on the label of the medicine or as set by the veterinary surgeon;

- Maintain an animal medicines record book on farm together with copies of relevant regulations and Codes of Practice;

- Accurately record the identity of the animals medicated, the batch number, amount and expiry of the medicine used, the withdrawal period required and the date and time the medication was completed;

- For all medicines used, appropriate information should be kept on file, for example, product data sheets, package inserts or safety data sheets as available;

- Report to the veterinary surgeon, (or in the case of a non-prescription medicine, the supplier, or direct to the Veterinary Medicines Directorate) any suspected adverse reaction to a medicine in either the treated animals or farm staff having contact with the medicine. This should include any unusual failure to respond to medication. A record of the adverse reaction should also be kept on the farm: either a copy of the VMD adverse reaction form or a note in the medicines record book;

- Co-operate with Farm Assurance schemes which monitor antimicrobial usage, medication documentation and withdrawal period compliance. However, such schemes should not constrain the farmer from preventing the suffering of his animals;

- With your veterinary surgeon monitor antimicrobial usage taking account of the potency of various products;

- Farmers and stockmen have responsibilities for the safe use, storage and disposal of medicines. These responsibilities include:

    - Storage
    - Administration techniques
    - Recording

- Withdrawal periods

This must be backed up by recording systems which are essential in providing a framework for identifying disease problems and allowing appropriate changes to management practices. This can lead to a reduction in antimicrobial use.

UKASTA: Feed Assurance Scheme

The UKASTA Code of Practice for the Manufacture of Safe Compound Animal Feeding Stuffs recognises that compound animal feeding stuffs are a significant link in the chain of production of food products derived from or produced by live animals. Feeding stuffs should be of consistent quality to meet expected performance standards and must protect both human and animal health.

The purpose of the Code is to define a set of principles for the production of safe animal feeding stuffs including the sourcing and evaluation of feed ingredients as well as manufacture, storage, loading, transport and delivery of the feeding stuffs themselves.

Special attention is also paid within the Code to the production of medicated and zootechnical feeding stuffs and the need for competent and trained personnel. A fundamental requirement of the Code is the need for adequate documentation.

Key areas covered by the Code are:

- HACCP
- Design and Maintenance of Manufacturing Sites and Plants
- Storage of ingredients and compound feeding stuffs
- Feed ingredients
- Manufacturing Principles
- Manufacturing Operations
- Loading, Transport and Delivery
- Quality Control
- Complaints
- Product Recall
- Personnel
- Documentation

14.2 UNITED STATES

14.2.1 The US Action Plan

In the United States an Action Plan (Public Health Action Plan to Combat Antimicrobial Resistance) was developed in 1999 by an interagency Task Force on Antimicrobial Resistance. The final version was published in January 2001. The Action Plan reflects a consensus of federal agencies on

actions needed to address antimicrobial resistance (AR), based on input from state and local health agencies, universities, professional societies, pharmaceutical companies, healthcare delivery organisations, agricultural producers, consumer groups and members of the public.

With respect to the prevention and control of antibiotic resistance in agriculture, the following objectives were identified:

- Improved understanding of the risks and benefits of antimicrobial use and ways to prevent the emergence and spread of resistance;
- Development and implementation of principles for prudent antimicrobial drug use in the production of food animals and plants;
- Improved animal husbandry and food-production practices to reduce the spread of infection;
- A regulatory framework to address the need for antimicrobial drug use in agriculture while ensuring that such use does not pose a risk to human health.

Further information can be obtained from:
www.cdc.gov/drugresistance/actionplan/

The latest move by the CVM in the United States is explained in a document released on 19 December 2000, entitled, "An Approach for Establishing Thresholds in Assocation with the Use of Antimicrobial Drugs in Food-Producing Animals". The document was discussed at a meeting held on 22-24 January 2001 in Rockville.

The prime concern is the possibility that the approved use of an antimicrobial drug in animals may give rise to resistant bacteria that in turn pose a risk to human health. As a consequence CVM is considering the establishment of regulatory thresholds to arrest the further emergence of resistant food-borne pathogens. Two types of thresholds are to be evaluated ~ a human threshold and a resistance threshold.

The human health threshold is the unacceptable prevalence of infections in humans that are treated with the antimicrobials of concern, are associated with bacteria resistance to that antimicrobial, and for which resistance is attributable to its use in animals. Based on the animal safety standards, the 'unacceptable prevalence' is considered that level at which there is no longer reasonable certainty that there is no harm to human health.

The resistance threshold is the maximum allowable prevalence of resistant bacteria isolated from animal-derived food that does not pose an unacceptable risk to human health. This resistance threshold is derived through an epidemiology-based model that describes the relationship between human health threshold and resistance levels in animals. If this approach is adopted, then when surveillance data indicate that the resistance threshold

has been exceeded, CVM would initiate procedures to withdraw from the label any animal species that had reached or exceeded its threshold.

Further information can be sourced from:
http://www.fda.gov/cvm/antimicrobial

14.2.2 AVMA: The American Veterinary Medicine Association Response to Antibiotic Resistance

The AVMA shares the concerns of the human medical community regarding the broad issue of antimicrobial resistance, and specifically, the potential risk of zoonotic pathogens developing resistance in animals with subsequent transfer to humans.

> " We acknowledge that the use of antimicrobial agents by veterinarians could possibly contribute to the development of resistance[21]. "

In November 1998, the Food and Drug Administration Center for Veterinary Medicine (FDA) announced that evaluating the human health impact of the microbial effects associated with all uses of antimicrobial drugs in food producing animals is necessary. A 'Framework Document' was released in December 1998 for public comment. This document set out a conceptual risk-based process for evaluating the microbial safety of antimicrobial drugs intended for use in food producing animals. The FDA recommends that antimicrobial drugs used in food animals would be categorised in a risk-based framework, according to their importance in human medicine, and the extent of potential human exposure associated with animal use. Drugs classified in restricted categories would be required to undergo pre-approval studies to assess the rate and the extent of resistance development in certain enteric bacteria. Post-approval resistance monitoring would also be required. If drug resistance in certain bacteria reached certain thresholds, mitigating actions would ensue, including as a last resort, withdrawal of approval of the drug for use in one or more species of animals.

The following statement sums up the position of the FDA:

> " The National Center for Infectious Diseases (NCDC) and Center for Disease Control (CDC) and prevention strongly supports the proposed FDA framework as an important step toward protecting public health while ensuring the availability of needed animal antibiotics[22]. "

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[21] The American Veterinary Medicine Association, (July 1999) *Responds to Antibiotic Resistance* The C.A.USE: 12: (3) U.S. Department of Health and Human Services

[22] FDA (1999) FDA Proposes *New Framework for Evaluating Antibiotics Used in Food Animals*: The C.A.USE: 12 (1) US Department of Health and Human Services

In June 2001, the American Medical Association approved a resolution advocating that the "non-therapeutic use" of antibiotics in animals should be phased out and eliminated.

14.2.3 Global Surveillance

CSR: Communicable Disease Surveillance and Response

A range of papers on antimicrobial resistance surveillance in foodborne pathogens was presented at the informal meeting at the WHO, headquarters Geneva, Switzerland, between the 31st March and 1st April 1999. Countries with surveillance networks in place include: Europe; USA; Canada; Caribbean; Denmark; Sweden; The Netherlands; Switzerland; Thailand and Japan. Just a few examples of surveillance networks presently implemented can be seen below.
Formerly the Division of Emerging and other Communicable Diseases Surveillance and Control (EMC) and programmes from the Division of Control of Tropical Diseases (CTD). WHO provides a neutral and international framework to co-ordinate and focus efforts of the many stakeholders in the field of resistance surveillance and containment.

The WHO Collaborating Centre working with CSR are building the Antimicrobial Resistance Information Bank (AR InfoBank). This is an electronic database of resistance data and surveillance networks which is being established to provide access, by policy-makers and health care workers, to quality information about drug resistance and resistance surveillance networks.

ENTER-NET

ENTER-NET is an international surveillance network for human gastrointestinal infections. When the network began it involved all 15 countries of the EU, plus Switzerland and Norway. The network conducts international surveillance on verocytotoxin producing *E. coli* (VTEC) 0157, including antimicrobial resistance.

The overall aim of the ENTER-NET project is to improve understanding of the extent and evolution of antimicrobial resistance in *Salmonella* isolates and of the distribution of VTEC 0157 infections within the EU.

A pilot study into the surveillance of antibiotic resistance testing results has been conducted between 18 national *Salmonella* reference laboratories. The outcome of the study shows that there is highly significant agreement between the results from national laboratories and has highlighted those areas that still require some development. This has demonstrated that meaningful antimicrobial resistance surveillance can be achieved successfully on an international basis.

At a recent meeting representatives from Australia, Canada, Japan, South Africa and the U.S. were also present. The network conducts international

surveillance on microbiological, epidemiological and policy aspects of infections caused by *Salmonella* and E. *coli* (VTEC).

Implementation of the European Commission's draft directive on zoonoses will result in Enter-net being responsible for annual reports on the human aspects of these zoonoses. ENTER-NET's legal obligation will be to ensure that *Salmonella* and VTEC infections, as well as antimicrobial resistance, are monitored and that outbreaks are investigated appropriately.

EARSS

European Antimicrobial Resistance Surveillance System (EARSS) is an international network of national surveillance systems, which aims to aggregate comparable and reliable antimicrobial resistance data from 400 participating laboratories from different member states, as well as from countries outside the EU. During 2001, 25 countries were participating.

EARSS provides incidence figures and trends in antimicrobial resistance, describes regional differences, and gives electronic feedback, providing basic data to stimulate specific studies to assess risk factors. EARSS acts at the same time as an incentive to improve national surveillance systems. EARSS started on 1 April 1998, and has continued since then. It is funded by DG SANCO of the European Commission.

NARMS

In the United States, a National Antibiotic Resistance Monitoring System (NARMS) was established by the FDA, Center for Disease Control and Prevention (CDC) and the US Department of Agriculture (USDA) because of public health concerns with the use of antimicrobials in food producing animals.

The aim of NARMS is to monitor changes in antimicrobial susceptibilities of zoonotic enteric pathogens from human and animal clinical specimens, from healthy farm animals, and from the carcasses of food-producing animals at slaughter. At the present time, NARMS is monitoring susceptibilities of *Salmonella* and *E. coli* isolates to 17 antimicrobics and *Campylobacter* isolates to 8 antimicrobics (azithromycin, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamycin, nalidixic acid, and tetracycline).

The data can provide useful information about patterns of emerging resistance, which in turn can help guide treatment decisions. NARMS data also supports outbreak investigation. Antimicrobial resistance patterns are useful in identifying the source and magnitude of resistance. Antimicrobial resistance data from humans and animals are important for the development of public health recommendations for the use of drugs in humans and food animals. (NARMS animals data is available on: fda.gov/cvm/antimicrobial).

CCCAR

Dr R Irwin, Food Programme Coordinator, Antimicrobial Resistance Project - Health Canada stated:

> "Surveillance systems to monitor resistance among foodborne bacteria from the human, animal and food sectors are needed in order to understand the magnitude and impact of antimicrobial resistance. These systems will ultimately provide policy makers and health professionals with timely information to detect and prevent the transmission of resistant bacteria and resistant determinants between animals and humans. It will also assist in the development of evidence-based guidelines for the prudent use of antimicrobials in animals and humans.
>
> Health Canada recognises that the ultimate control of antimicrobial resistance will require concerted actions in both the medical and agricultural communities. As a starting point Health Canada sponsored a Canadian Consensus Conference Controlling Antimicrobial Resistance: An integrated action plan for Canadians in May 1997. In response to recommendations from this conference, Health Canada has established the Canadian Coordinating Committee on Antimicrobial Resistance (CCCAR)."

The mandate of this Committee is:

- to promote the development and implementation of strategies;
- to focus efforts of health-care providers, industry and Canadian consumers toward the goal of more effective use of antibiotics; and
- to limit the development and transmission of antimicrobial resistant bacteria.

The strategy is based on achieving four main goals:

1. Maximize surveillance capability.
2. Maximize prevention of infection capability.
3. Ensure appropriate usage of Antibiotics.
4. Strengthen partnerships.

It is impossible to address the threat posed by antimicrobial resistance without knowledge of the types and characteristics of antimicrobial resistance that are occurring. To develop this type of knowledge, it is critical that appropriate surveillance systems be established.

The following key strategies have been developed to achieve this objective:

1. establish a national integrated surveillance system for resistant organisms related to humans and animals;

2. establish a national integrated surveillance system of antimicrobial use for humans and animals;

3. establish national standards for laboratory testing for identification of antimicrobial resistance;

4. study the impact of antibiotic use and resistance in human and animal health;

5. establish mandatory reporting of certain infectious diseases caused by antimicrobial resistant organisms;

6. conduct research (targeted surveillance studies) to better understand the epidemiology of antimicrobial resistance in humans and animals.

To initiate discussions on the issue of antimicrobial resistance with stakeholders from the agriculture and aquaculture sectors in Canada, Health Canada convened a stakeholder workshop in June of 1998. The objective of this workshop was to review the recommendations of the World Health Organisation, and initiate steps to carry out these recommendations in three key areas ~ prudent use policies, surveillance and research. The next step in this surveillance initiative is being undertaken under the leadership of the Laboratory Centre of Disease Control.

CVMA (Central Veterinary Medical Association) have issued a set of general and specific principles available from: www.ccar-ccra.org

The Central and South America and the Caribbean Collaborative Project on Surveillance of Antimicrobial Resistance in Salmonella, Shigella and *Vibro cholerae*

For the past four years, the Communicable Diseases Program of the Pan American Health Organization (PAHO), in collaboration with the Laboratory Center for Disease Control of Canada, has been sponsoring a project to strengthen the monitoring of resistance to antimicrobials in certain enteropathogen agents.

The overall purpose of this project is:

To improve the epidemiological and laboratory infrastructure and the expertise needed to carry out surveillance of *Salmonella, Shigella* and *Vibrio cholerae* species, in order to asses the magnitude of the problem.

Specific objectives:

Strengthen laboratory capacity and standardize methodologies for diagnosing *Salmonella, Shigella* and *Vibrio cholerae* at present, and pathogenic Escherichia coli in the future;

Strengthen epidemiological surveillance systems and develop a data base on antimicrobial susceptibility of selected enteropathogens;

Establish a national reference laboratory network for the diagnosis of these enteric pathogens;

Formulate effective national programmes in order to prevent and contain the resistance of infectious agents to antimicrobials.

Several workshops have been held in order to standardize techniques for assessing antibiotic sensitivity, protocols for quality assurance, proficiency testing and epidemiological surveillance. Representatives from Argentina, Brazil, Colombia, Chile, Costa Rica, Mexico, Peru and Venezuela participated in the workshops. Training in laboratory techniques and use of the Public Health Laboratory Information System (PHLS) was provided by participants from the Laboratory Center for Disease Control (LCDC) of Canada and the Centers for Disease Control and Prevention (CDC) of the United States. The above mentioned participants recommended that professionals from Bahamas, Barbados, Jamaica, Saint Lucia, Suriname and Trinidad and Tobago also be trained. In order to standardize test materials used by different countries, antibiotic disks and dispensers were provided and were used to evaluate sensitivity retrospectively and prospectively. Other reagents were also provided. The LCDC prepared and distributed samples for performance evaluation and analyzed the results.

In January 1998, professionals from participating laboratories in Latin America and Canada met in Mexico City to analyze the results of quality control activities and sensitivity tests to antimicrobial drugs (for isolates of *Salmonella, Shigella* and *Vibrio cholerae*) obtained from the laboratory network during 1997. During this meeting the countries agreed to submit quarterly surveillance reports to PAHO to be published on its website. The LCDC also agreed to: a) evaluate quality control measures on the antisera; b) provide training, and c) to provide countries with protocols and necessary sources of reference. Evaluation visits and seven workshops for standardizing procedures and epidemiology have also been carried out, as well as the review and analysis of data generated by the project, and techniques for the identification of *Escherichia coli* 0157:H7.

Two meetings were held in February 1999 and 2000 in Winnipeg, Canada, and Santiago, Chile respectively, to evaluate the activities and progress made on the project during 1998 and 1999.

The data referring to *Salmonella, Shigella,* and *Vibrio cholerae* resistance provided by the countries was submitted to PAHO and consolidated and published on PAHO's web site: www.paho.org.

JETACAR

In Australia, the two recommendations put forward by the JETACAR report regarding monitoring and surveillance were as follows:

1. That a comprehensive surveillance system be established incorporating passive and active components measuring incidence and prevalence of antibiotic-resistant bacteria and resistance genes, covering all areas of antibiotic use; and

2. That a comprehensive monitoring and audit system for antibiotic usage be established that covers all areas of antibiotic use.

The Australian Government's response to both these recommendations was positive. In particular the Government is in favour of the concept of improving the surveillance of antibiotic-resistant bacteria and resistance genes across the food chain and in human medicine, however it does emphasise the importance of further investigations to determine the most appropriate and cost-effective option for national integration of animal and human surveillance data. The Government supports the principles of accountability and audit trail inherent in the second recommendation above.

OIE International Conference on Antimicrobial Resistance

In October 2001, a second International Conference on Antimicrobial Resistance, the use of antimicrobials and protection of public health, was held at the OIE Headquarters in Paris.

The following guidelines on antimicrobial resistance were presented:

- Risk analysis methodology for managing the potential impact on human and animal health of resistant bacteria of animal origin due to use of antimicrobials in animals;

- Prudent use of antimicrobials in veterinary medicine and surveillance and monitoring of antimicrobial quantities used in animal husbandry;

- Harmonisation of national antimicrobial resistance surveillance and monitoring programmes in animals and animal-derived food;

- Standardisation and harmonisation of laboratory methodologies used for the detection and quantification of antimicrobial resistance.

15.0 VETERINARY MEDICINES

15.1 Prescription & Supply in the United Kingdom

In the UK veterinarians are allowed to supply veterinary medicines which they have prescribed. The Advisory Committee commented on the issue as follows:

> " It is for consideration whether the sale of veterinary medicines by prescribing veterinarians raises usage of veterinary medicinal products to levels higher than they would otherwise be and than are justified, and promotes the use of these products at the expense of good farming practice. The sources of income in veterinary practice have changed considerably since World War II. While major eradication schemes against tuberculosis and brucellosis were in progress, veterinary practices were able to derive about one-third of their incomes from local veterinary inspector (LVI) fees and the rest from professional fees and drug sales. In the 1950s and 1960s, however, many free sources of advice became available to farmers who were thus less inclined to pay for veterinary advice. In consequence, veterinary charges were skewed so that the decline in income from professional fees was offset by an increase in income from drug sales. At the present time, the LVI component of practice income has probably reduced to less then 5% for farm veterinarians. Drug sales account for possibly some 40% of income, however, this figure covers all drugs, including anthelmintics. At present, the mark up is probably higher on prescription only medicines (POMs) than on pharmacy and merchants' list (PML) products and feed antibiotics. "

It recommended that:

> " The veterinary profession must address this problem by introducing rapidly a code of practice on when such compounds should be prescribed (e.g. when other agents have failed) and how (e.g. for no longer than necessary)."

15.1.1 Review of Dispensing of Medicines by Veterinarians

In August 2000, the British Government established an Independent Review of Dispensing by Veterinary Surgeons under the chairmanship of Sir John Marsh. The terms of reference were:

- To review the procedures by which prescriptions only medicines (POMs) for veterinary use are classified and sold in the United Kingdom and the impact current practices may be having on availability and prices.

The Review Group found that there is lack of transparency in the prices paid by clients for animal medicines. Many clients are unaware that they may request a prescription from a veterinarian than can be dispensed by a pharmacy. The Group recommended that when veterinarians prescribe medicines that they should be required to provide a written prescription which can be dispensed by any suitable qualified person.

The Group noted that the margin which a veterinary practice adds to the price at which the medicines have been purchased is not visible to the client. Furthermore veterinarians derive a significant part of their total income from the sale of veterinary medicines. It is considered acceptable practice for professional fees to be 'underpinned' and for the cost of medicines to be overpriced. The reason for this is that it is believed farmers are reluctant to pay for advice but willing to accept a relatively high cost for medicines.

Although not specifically addressed by the Review Group, there must be a strong suspicion that this practice encourages the prescription and sale of veterinary medicines. Unless a veterinarian actually prescribes and supplies a medicine, he/she will not receive adequate recompense for providing advice.

RELEVANT RECOMMENDATIONS FROM THE MARSH REPORT PLUS THE INTERIM RESPONSE FROM THE GOVERNMENT

During December 2001, the Government issued its initial response to the recommendations of the Marsh report.

The relevant ones are as follows:-

Recommendation: We recommend that veterinarians having made a diagnosis and prescribed medicine, should be required to provide a written prescription, at either no additional charge or at a fee to be determined by the RCVS (Royal College Veterinary Surgeons) acting in the public interest. Clearly this recommendation would not apply where emergency treatment is needed, for treatments during surgical procedures or the use of anaesthetics.

Interim Response:

The Government accepts that the client should be able to choose where he/she buys a POM for their animals. To achieve this the client should be offered a written prescription by the veterinary surgeon. The Government would prefer to introduce this change by strengthening the professional guidance, rather than by legislation.

The Government accepts that veterinary surgeons should be able to charge for providing a prescription in the same way as they can charge for any other service they provide. Fees are normally set between the veterinary surgeon and the client and this would apply to a fee for writing a prescription.

Recommendation: We recommend that the Minister should consider moving in the longer term towards adopting a system of classification that has two major categories. Prescription-only Medicines and General Sale List Products. We would suggest that the POM category should be divided into three sub-groups as follows:

POM (A) - medicines which may be administered only by a veterinary surgeon or under his/her direct supervision. In the latter instance the

veterinary surgeon should be present at the time of administration and in a position to render assistance if necessary.

POM (B) – medicines which may be sold or dispensed by a veterinary surgeon to animals under his/her care after a prior clinical examination of the animal or animals; or sold or dispensed in a pharmacy in response to a written veterinary prescription.

POM (C) – medicines which may be sold or supplied by veterinarians for administration to animals under their care, or by pharmacists or, providing the purchaser can demonstrate evidence of competence in their use, by registered agricultural merchants. For this group of products a prior clinical examination of the animal(s) is not a requirement, however in cases where no evidence of competence is available the products in this category should only be made available by pharmacies, registered agricultural merchants or other registered outlets against a written prescription from a veterinarian.

Interim Response:

The present classification and distribution system in the UK has worked well for many years. There is no evidence that it has led to abuse of veterinary medicines or to residue violations that would harm the consumer. As part of its proposals following the review of medicines legislation in Europe (Review 2001), the European Commission has subsequently proposed changes to the distribution system for veterinary medicines, most significantly, that all medicines for food producing animals should be classified POM. If this was accepted by a majority of member states then the independent review team's proposal could serve as a model and retain the benefits of the current distribution arrangements. The Government will however argue for more flexibility in the Commission's proposals so that Member States can take advantage of existing arrangements as long as consumer protection and animal welfare can be demonstrably assured.

Recommendation: We recommend that prescriptions written by veterinarians should be dispensed by any suitable qualified person, including the prescribing veterinarian, other veterinarians, pharmacies and, in the case of POM (C) products, by persons holding AMTRA, SQP qualifications and employed by registered agricultural merchants and other registered retail outlets.

Interim Response:

The Government supports this recommendation which would give the client the widest choice of appropriately qualified people to dispense a prescription. Implementation would require amending legislation.

Recommendation: We recommend that farmers and veterinarians join with pharmacists, agricultural merchants and farm management advisors to create health plan for farm animals, within which medicines can be supplied at least cost.

Interim Response:

The Government would encourage the various interests involved to work together to stimulate the development of farm health plans with the objective of improving the health of flocks and herds thereby reducing the need for therapy.

15.1.2 Office of Fair Trading Investigation

The Office of Fair Trading (OFT) is investigating complaints that prices of POMs in the UK are higher than in other countries. Veterinary surgeons have been asked to provide information on how much they are being charged by the manufacturers. This request carries the weight of law and those practices which have been approached must respond. Information on 3 years of drug purchasing is being requested. The drugs bought must be split into categories. Information on incentives schemes and discount obtained for the different suppliers must be provided.

At the same time the BVA has conducted its own survey on the pricing of veterinary medicines which was based on 750 randomly selected parties. Preliminary results indicate a 'mark up' of about 33%. The big question to be faced is 'does the mark up encourage the prescription of drugs as opposed to other forms of treatment/preventions which do not involve the use of veterinary medicines?'

In October 2001, the Director General of Fair Trading asked the Competition Commission to inquire into the Supply of POMs within the UK. In particular it was asked to investigate whether a complex monopoly situation exists in this sector and, if so, whether it operates, or may be expected to operate, against the public interest.

15.1.3 Sources of Supply for Veterinary Medicines

In the United Kingdom, animal medicines are classified into one of the following groups:

- Prescription only Medicines (POM) which can only be supplied when a veterinarian has issued a prescription;
- Pharmacy & Medicines List (PML) ~ the distribution is controlled through qualified and registered agricultural merchants, veterinary practices (to their own clients) and from pharmacies;
- General Sales List (GSL) which are widely available.

In order for an agricultural merchant to register, sell and supply PML medicines, the business must nominate a suitably qualified person to be responsible for the sale of the animal medicines. Proposed new EU legislation would require all health products for food animals to be sold as POMs. This is being strongly opposed by UK interests who argue that this change would

increase costs to farmers and make it more difficult to obtain products which are currently classified as PMLs.

Many in the veterinary profession and the animal health industry are concerned that if there is reclassification of POMs, and changes in the actual supply, then the income of vets would be adversely affected. It is argued that the current system protects animal health and welfare by ensuring that the right medicines are available for appropriate use when needed. The case is also being made that vets have a vital role to play in protecting public health by ensuring veterinary medicines are used safely and responsibly.

15.1.4 The Competition Commission and the Veterinary Medicines Monopoly Inquiry

The Competition Commission recently released a statement, in April 2002, setting out the issues which the Competition Commission is currently considering in connection with its inquiry into the supply of prescription-only veterinary medicines in the United Kingdom.

This statement sets out one provisional conclusion and a number of other issues, which it is still considering and the Commission is aiming to submit its full report by January 2003.

The issues statement covers all participants in the medicines supply chain, from manufacturers and regulators, through to the end user and although the Commission acknowledges that many of the practices discussed may be inter-related, the issues are divided into four main groups:

- Issues arising from the regulatory regime, which governs the supply of prescription-only medicines in the United Kingdom;
- Issues stemming from the practices of veterinary manufacturers;
- Issues stemming from the practices of the veterinary wholesalers, and
- Issues stemming from the practices of veterinary surgeons.

A copy of this statement of issues can be found on the Commission's website: www.Competition-Commission.org.uk/inquiries/vetmed.htm

At a public hearing, as part of the Competition Commissions' investigations held in London on 26th April 2002, a representative from the NFU said: "The time has come for the Veterinary profession to take the opportunity, given the circumstances special to agriculture at the moment, to levy proper fees and learn to sell their services. Instead of providing emergency services the profession should look to service contracts with farmers, herd health plans etc as recommended in the Policy Commission on Farming and Food. By

working in partnership in this way, vets and farmers could develop a far better approach to animal health." [23]

15.2.1 Monitoring Residues

Denmark

These results confirm that the Danish pig industry continues to be successful in keeping the presence of residues down to a minimum (Table 15.2.1)

Table 15.2.1: Residues in Danish pigmeat

Year	No. of Slaughter Pigs (Millions)	Random Samples (No.)[a]	Positive Samples (No.)	Positive Samples (%)
1989	15.3	19,371	15	0.08
1990	15.7	15,816	10	0.06
1991	16.2	17,061	2	0.01
1992	17.8	17,350	1	0.01
1993	19.1	19,100	6	0.03
1994	19.7	20,139	6	0.04
1995	19.7	20,091	5	0.02
1996	19.5	19,802	3	0.02
1997	20.4	19,483	6	0.03
1998	20.3	20,509	3	0.01
1999	20.4	21,154	4	0.02
2000	20.9	20,474	3	0.02
2001[b]	20.9	21,914[c]	1	0.005

(Danske Slagterier, September 2001)

[a] *Antibiotics and chemotherapeutics* ~ including blood samples examined for sulphonamides.

[b] From May 1st 2001, the presence of antibiotics in meat for human consumption has been monitored by the Danish abattoirs.

[c] Of the 21,914 samples tested, 9,720 were by the statutory bodies and 12,194 by the abattoirs.

15.2.2 United Kingdom

On March 14, 2000, Baroness Hayman (Food Safety Minister at DEFRA) announced the plan to replace the Advisory Group on Veterinary Residues (AGVR) with the Veterinary Residues Committee (VRC). This committee will be independent of the Government and comprise a chairman and 12 members which shall form a strong mix of consumer, scientific and food industry expertise (The Veterinary Record, March 18, 2000). Recent data on veterinary residues are shown in Table 15.2.2

In 2000, sulphadimidine residues were found in 5 out of 1,053 pig samples. Chlortetracycline residues above the MRL were found in 7 out of 1,400 pig

[23] Veterinary Record, 4 May 2002 pp 560

kidney samples tested. The incidence (0.5%) is the highest reported over the last 4 years.

Table 15.2.2: Residues in UK slaughter pigs

	Antimicrobials			Sulphonamides			
Year	Random Samples (No.)	Positive Samples (No.)[a]	Positive Samples (%)	Random Samples (No.)	Positive Samples (No.)[b]	Positive Samples (%)	Total Positive Samples (%)
1993	12,412	40	0.32	1,183	18	1.52	0.43
1994	12,713	25	0.19	1,172	21	1.79	0.33
1995	12,839	40	0.31	1,063	15	1.41	0.40
1996	10,143	56	0.70	943	17	1.7	0.66
1997	11,404	29	0.25	1,047	11	1.05	0.32
1998	1,584	1	0.06	939	4	0.43	0.20
1999	1,646	0	0.00	1,460	3	0.21	0.10
2000	1,400	7	0.50	1,053	5	0.47	0.49
2001	1,240	8	0.65	1,030	3	0.29	0.48

(MAVIS)

[a] Positive Samples (No.) = Number above the MRL
[b] In all cases, sulphadimidine was detected

The position in the UK was showing improvement up to 1999, but in 2000 it appears to have deteriorated.

15.2.3 Impact of Food Standards Agency in Great Britain on the approach to residues

Although responsibility for policy on veterinary medicines remains with the Veterinary Medicines Directorate, the newly established Food Standards Agency is the watchdog for food safety. Thus the Agency has been given powers by the Food Standards Act 1999 to ensure that it plays an effective role in the regulatory process for veterinary medicines. It also has the same role in relation to pesticides which fall under the responsibility of the Pesticides Safety Directorate.

The relevant policy of the FSA is as follows:

> "We accept the use of pesticides and veterinary medicines in the production of food if:
>
> - regulatory bodies follow a precautionary approach;
> - the independent scientific advice is that safety is within acceptable limits;
> - acceptable levels can be set for residues in food; and

- enough good quality information is available on which to base these decisions.

We believe that consumers have a right to expect that any residues that occur in foods should:

- not be harmful; and

- be as low as practically possible, even if higher levels would still be safe.

Where there is clear evidence of misuse, the FSA will press for strong action to protect consumers. Where surveillance finds residues above acceptable levels for other reasons, we will ensure that prompt, effective action is taken to identify and rectify the problem. When new data become available, we will revisit previous decisions."

16.0 DISPOSAL OF VETERINARY MEDICINES

16.1 United Kingdom

The disposal of medicines is regulated under the Control of Substances Hazardous to Health Regulations 1988. There are two categories of waste ~ clinical or pharmaceutical. The Special Waste Regulations 1996 implements the EU Directive 91/689/EEC. Within the UK, prescription only medicines are classed as 'special wastes'. All 'special wastes' are tracked during movement to a waste management facility. The Environment Agency enforce compliance with these regulations.

Unused antibiotics should be returned to the veterinarian for disposal as pharmaceutical waste. The Advisory Committee observed that medicated feed is rarely disposed of in this way. Excess medicated feed often appears to be fed to the next batch of animals. In Denmark, under the Health Advisory Agreement, veterinarians remove all unused pharmaceutical products from the farm and dispose of them.

17.0 HEALTH CARE PLANS

17.1 United Kingdom

The Advisory Committee recommended 'that Government encourages regular veterinary visits to all livestock farms or production units to audit animal disease profiles and general performance indicators, to accumulate and scrutinise morality, morbidity and general health data, and to record antibiotic resistance patterns so that antibiotic prescribing can be adjusted accordingly.'

The Government accepts this recommendation and will encourage veterinarian visits. This corresponds to what the Danes presently undertake. The 'Code of Practice on the Responsible Use of Animal Medicines on the farm' leaflet by the VMD addresses many of these issues.

Since the Advisory Committee's Report there has been a significant increase in the uptake of voluntary Farm Assurance Schemes, which have their own rules and regulations on medicines, implementing an annual audit and quarterly visit from veterinarians.

Many animal production units are now members of such schemes. These assurance schemes are run by the industry and are not regulated by Government bodies. The Government will, however, undertake to encourage the growth of farm assurance schemes. Furthermore, the necessity of regular visits is being emphasised by both the BVA Codes of Practice and the RCVS Guide to Professional Conduct. This recommendation will be brought to the attention of the BVA and RCVS by the Government.

17.2 Denmark

A health advisory agreement is mandatory in herds regularly using medicine. The agreement must be approved by the Danish Veterinary Service. A health advisory agreement comprises of twelve visits during a year, i.e. six regular health advisory visits and six evaluation visits. The farm should be visited at least every 35th day. Only the herd veterinary surgeon or another approved veterinary surgeon can give the health advice.

A regular health visit includes:

- a clinical evaluation of the animal health status;
- recording and evaluation of health data;
- identification of herd problems;
- removal of left over medicine;
- prescription of antibiotics for up to 35 days treatment for a previously diagnosed bacterial infection;
- a written report, which includes:
    - herd health status
    - prescribed medicine (type, amount, diagnosis)
    - withdrawal period
    - number of animals under treatment

- amount of medicine in the herd.

In herds with a health advisory agreement, only the herd veterinarian can prescribe antibiotics for use up to 35 days. The farmer is allowed to administer antibiotics to sick animals following instructions given by a herd veterinarian for up to 5 days on each animal. In cases of acute disease another veterinary surgeon can prescribe antibiotics for acute treatment for up to a maximum of 5 days treatment.

An evaluation visit includes:

- evaluation of health progress;
- evaluation of medicine use;
- prescription of medicine;
- removal of left over medicine.

When the farmer administers medicine to production animals, the farmer must record:

- which animal was treated;
- date for start and end of treatment;
- the antibiotic used;
- the diagnosis given by the veterinary surgeon;
- doses and route of administration;
- person carrying out the treatment.

The Danish Veterinary Service randomly selects a number of farms on an annual basis for inspection under the health advisory agreement report in order to control the use of medicine and the actual amount and type of medicine found on the farm.

18.0 RECENT DEVELOPMENTS

Action on the regulation of the Fluoroquinolones

In 1995 and 1996, the FDA and Center for Veterinary Medicine (CVM) in the United States allowed the approval of enrofloxacin (a fluoroquinolone) for use in poultry. When approval was granted, the CVM believed that enrofloxacin could be used safely in poultry, and that resistance could be limited by certain restrictions. In October 2000, however, the CVM put forward a proposal to

withdraw approval for the use of enrofloxacin in poultry, because recent research had demonstrated that:

- The use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant Campylobacter (a human pathogen) in poultry;

- The fluoroquinolone-resistant Campylobacter is transferred to humans and is a significant cause of the development of fluoroquinolone-resistant Campylobacter infections in humans;

- Fluoroquinolone-resistant Campylobacter infections are a hazard to human health. Because of these considerations the CVM had decided that its only option to protect human health was to withdraw the approval. The product is not safe as provided for in the Federal Food and Cosmetic Act. Full details of the case prepared by CVM are shown in the US Federal Register, 31 October 2000.

Two companies, Abbott Laboratories and the Bayer Corporation, produce the enrofloxacin in the US. Abbott decided to withdraw the antibiotic as soon as the FDA proposal was announced.

Concern about antibiotic resistance is certainly growing in the United States.

In October 2001, the influential New England Journal of Medicine carried an editorial which agreed that antibiotic growth promoters contributed to the problem of antibiotic resistance and agreed that the practice should cease. In November, the US House of Representatives approved an additional $3 million for the Food and Drug Agency (FDA) for work to combat antibiotic resistance.

The current position indicates that the FDA is now planning to hold an administrative hearing to consider the forced withdrawal of Baytril, a fluoroquinolone manufactured by Bayer.

This stems from the proposal by the US Center for Veterinary Medicine (CVM) to ban the use of all fluoroquinolones for the treatment of poultry. The proposal was formulated because of fears that the use of Baytril in farm animals could lead to the development of resistance in human pathogens to antibiotics such as ciprofloxacin.

Other research work conducted by the CVM suggests that the increase in fluoroquinolone-resistant Campylobacter is due, in part, to the use of fluoroquinolones in poultry. In separate experiments, the effects of serafloxacin and enrofloxacin treatment of chickens infected with *Campylobacter jejuni* were measured. Faecal samples were collected before and after treatment and cultured for *C. jejuni*. When enrofloxacin or serafloxacin was used as approved in broilers, resistance developed rapidly and persisted in *C. jejuni*. These findings demonstrate that the use of these antibiotics in poultry rapidly selects for resistant Campylobacter organisms.

This could mean that fluoroquinolone therapy may not be effective for treating cases of human campylobacteriosis from exposure to contaminated chicken[24].

The Consumer Perspective

In the US some of the consumer groups have been taking a considerable interest in the antibiotics debate. A number, including the influential Centre for Science in the Public Interest, have joined together to organise a campaign called, "Help Save Antibiotics". Members of the organisations involved are being urged to:

"...work with Congress and the FDA to ban the use of medically important antibiotics in healthy livestock and poultry."

The medical profession is increasingly finding that bacterial infections do not respond to antibiotic therapy. A major reason for this is that antibiotics are being fed to healthy farm animals to promote growth and to compensate for unsanitary conditions in factory farms.

The concerns about the use of antibiotics in farm animals are beginning to have an impact on some of the major food producing companies. Chicken producers, Tyson Foods, Foster Farms and Perdue Farms, have voluntarily removed most or all of the antibiotics fed to healthy chickens. The awareness of the issue has been heightened by the anthrax scares because the fluoroquinolone, ciprofloxacin, has been used to treat anthrax. McDonalds is now refusing to accept poultry that has been treated with ciprofloxacin.

Recent research in Taiwan and Spain

In Taiwan, Chiu et al[25], found that enrofloxacin is added to pig feed as a growth promoter by half of the feed-mill operators which were surveyed. This would explain why 60% of isolates of *Salmonella enterica* Serotype Choleraesuis were resistant to ciprofloxacin. Molecular typing studies with patients infected with ciprofloxacin-resistant *Salmonella enterica* Serotype Choleraesuis found that the primary source of this infection was pigs, which provides convincing evidence that the resistant pathogen had originated in pigs.

In Spain, Mateū et al[26] isolated 155 strains of *Salmonella* from healthy and diseased pigs in order to determine the antimicrobial susceptibility profiles.

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[24] McDermott, Patrick F *et al: Ciprofloxacin resistance in Campylobacter jejuni evolves rapidly in chickens treated with fluoroquinolones*: Journal of Infectious Diseases (2002); 185: 837-840

[25] Chiu, Cheng-Hsun *et al*: (2002) *The Emergence in Taiwan of Fluoroquinolone Resistance in Salmonella enterica Serotype Choleraesis*: N Engl J Med: 346: 6: 413-419

[26] Mateū, E.M. *et al* (2002) *Antimicrobial susceptibility of Salmonella strains isolated from swine in Catalonia, Spain*: Veterinary Record: 150: 147-150

The antimicrobial susceptibility tests showed that most strains were resistant to tetracycline (84.2%) sulphonamides (81.6%) or ampicillin (74.5%) regardless of the serovar. Antimicrobials to which more than 50% of the strains were found to be resistant were chloramphenicol (57.5%) nitrofurantoin (53.0%) trimethoprim (52.7%).
The authors conclude that the results indicate that antimicrobial resistance is a real problem in pig isolates of *Salmonella*. This may be due to excessive use of antimicrobials in pigs.

The Swedish Experience

In 1986, Sweden banned the use of AGPs. As a consequence there were significant clinical problems which created a demand for therapeutic doses of antibiotics. This meant that the total amount of antibiotics used in annual production in Sweden increased from about 25.7 tonnes to almost 30.2 tonnes. Subsequently a number of measures were taken which reduced the gastro-intestinal problems in the pigs. These included a reduction in the protein content of the feed, the use of water-soluble fibres and supplementation with acids. It was also found that adding 2000 ppm of zinc oxide to the feed, starting 2 weeks before weaning, could help to prevent weaning diarrhoea.

By 1999, total usage of antibiotics was reduced to 18.3 tonnes which compared with a value of 50.5 tonnes being used in 1984.

19.0 WHO

The WHO Guidelines for national governments to reduce the need for antimicrobials in animal production are listed in Section 7.0. Below are some of the facts which were taken into consideration by WHO in establishing its position.

1. Inadequate understanding and training on appropriate usage guidelines, and the effects of inappropriate antimicrobial use on resistance, are common among farmers, veterinary prescribers and dispensers.

2. The largest quantities of antimicrobials are used as regular supplements for prophylaxis or growth promotion in the feed of animal herds and poultry flocks. This results in the exposure of a large number of animals, irrespective of their health, to frequently subtherapeutic concentrations of antimicrobials.

3. A lack of diagnostic services and their perceived high cost means that most therapeutic antimicrobial use in animals is empiric, rather than being based on laboratory-proven disease. For animals and birds that are farmed in large herds or flocks, the identification of a few ill individuals generally results in the entire herd or flock being treated to avoid rapid dissemination and stock losses.

4. Veterinarians in some countries earn as much as 40% or more of their income by the sale of drugs, so there is a disincentive to limit antimicrobial use.

5. Inefficient and inadequately enforced regulatory mechanisms regarding antimicrobial supply contribute to excessive and inappropriate drug use. Discrepancies between regulatory requirements and prescribing/dispensing realities for animal antimicrobial use are often worse than in human medicine.

6. Antimicrobials that are used as growth promoters are generally not even considered as drugs and are either not licensed or licensed solely as feed additives.

7. The marketing practices for antimicrobials, used by private industry, covering the therapeutic, prophylactic or growth promoter purposes in animals, influence the prescribing patterns and behaviour of veterinarians, feed producers and farmers.

8. In North America and Europe it is estimated that about 50% in tonnage of all antimicrobial production is used in food-producing animals and poultry.

9. The increased intensity of meat production under crowded industrialised conditions contributes to the increased use of antimicrobials since they are used in subtherapeutic doses as growth promoters and used therapeutically for the treatment of infected animals.

10. The impact of antimicrobial metabolites and non-metabolised drug in animal sewage, that is released into the environment, is not clear.

11. Scientific data strongly suggests that avoparcin use in animals contributes to an increased pool of vancomycin-resistant enterococci (VRE).

12. VRE cause serious infections, mainly in hospitalised immunocompromised patients. Such infections are difficult to cure due to the limited number of effective treatment options and are thus associated with increased morbidity and mortality.

13. Studies in Denmark have shown that the ban on avoparcin in animals has led to a reduction in the prevalence of VRE in poultry and pigs. Studies in Germany and the Netherlands suggest that banning avoparcin has led to a reduction in the prevalence of VRE in healthy individuals in the community.

14. Sweden banned the use of growth promoters in livestock and poultry in 1987 and focused on the implementation of disease prevention methods that did not involve antimicrobials and on the prudent use of

antimicrobials for therapeutic purposes. The subsequent national antimicrobial consumption has reduced by approximately 50%. Furthermore, the prevalence of antimicrobial resistance in pathogenic bacteria isolated from animals in Sweden has been maintained at a low level since 1985.

15. Following the introduction of fluoroquinolones for use in food-producing animals, the emergence of *Salmonella* serotypes with reduced susceptibility to fluoroquinolones has been observed in countries such as France, Germany, Ireland, the Netherlands, the Russian Federation, Spain and the UK.

16. The introduction of fluoroquinolone use in poultry has been associated with a dramatic rise in the prevalence of fluoroquinolone-resistant *Campylobacter jejuni* isolated in live poultry, poultry meat and from infected humans. Prior to fluoroquinolone use in poultry, no resistant strains were reported in individuals without previous exposure to these agents.

GLOSSARY

ACMSF: Advisory Committee on the Microbiological Safety of Food.

ACNFP: Advisory Committee on Novel Foods and Processes

AGVR: Advisory Group on Veterinary residues

Antibiotic: a substance, produced by or derived from a micro-organism, which selectively destroys or inhibits the growth of other micro-organisms. Because compounds such as sulphonamides and quinolones are synthesised chemically, they are not strictly antibiotics. In practice, however, the term "antibiotic" often encompasses such agents and this broader view has been adopted in the terminology used in this Report.

Antibiotic Growth Promoters: also called Zootechnical Feed Additives.

Those below are approved for use in the EU:

Flavomycin: is presented in granular form for application as a top dressing addition to animal feeding stuffs of pigs, poultry and cattle. Flavomycin is also on the market under product names of Flaveco.

Monensin: under the product name Romensin, Elancoban and Ecox. Romensin G100 is used for growth promotion in cattle. Elancoban G200 is used prophylactically in poultry production.

Salinomycin: under the product name of Sacox, Kokcisan, Salocin, Bio-cox, Saleco and others. Sacox is used prophylactically in chickens. Salocin is presented in granular form to be incorporated in feed, for use in growing and fattening pigs.

Avilamycin: is presented in granular form for addition to animal feeding stuffs in pig and poultry production. Avilamycin is also on the market under the product name of Maxus.

Antibiotic Resistance: the ability of a micro-organism to withstand an antibiotic.

Antimicrobial: a compound which, at low concentrations, exerts an action against micro-organisms and exhibits selective toxicity towards them. The term Antimicrobial includes any substance of natural, synthetic or semi-synthetic origin which is used to kill, or inhibit the growth of, micro-organisms (bacteria, fungi, protozoa and viruses). Antimicrobials include antibiotics, disinfectants, preservatives and other substances (e.g. Copper, zinc).

Acquired Resistance: resistance to an antibiotic which develops in micro-organisms which were previously sensitive.

Broiler: a chicken reared for its meat.

BVA: British Veterinary Association

Classification of Veterinary Drugs:

GSL: General Sale List - veterinary drugs that may be sold through any retail outlet.

PML: Pharmacy and Merchant List - veterinary drugs that may be sold by pharmacies and registered agricultural merchants.

POM: Prescription Only Medicine - veterinary drugs which may only be sold or supplied by retail in accordance with a prescription given by a veterinary surgeon or veterinary practitioner.

ZFA: Zootechnical Feed Additives - formally classified as PML feed additives but are no longer considered as medicines under the Medicine Act and are controlled and authorised under EC legislation, Directive 70/524/EEC. ZFAs are substances such as antibiotics, trace elements, enzymes etc which are added to animal feeds to increase productivity. When used as ZFAs, copper salts and antibiotics greatly reduce the population of commensal micro-organisms. This reduces cellular activity and increases the net absorption of nutrients. An in-feed antibiotic also reduces the problems of low-grade infection with bacteria sensitive to that antibiotic. ZFAs increase the risk of infection with bacteria resistant to the antibiotic by impairing the probiotic effects of the natural flora.

CCCAR: Canadian Consensus Conference Controlling Antimicrobial Resistance

CDC: Center for Disease Control

Coccidiostats: products used for the control of coccidiosis, a protozoal disease causing diarrhoea and dysentry.

Commensal: an organism which derives benefit from living in close physical association with another organism, the host, which derives neither benefit nor harm from its relationship with the commensal.

Cross-resistance: resistance to several individual antibiotics, either of the same class or of different classes, due to a single resistance mechanism.

CVMA: Central Veterinary Medical Association

DEFRA: Department for Environment, Food and Rural Affairs

EARSS: European Antimicrobial Resistance Surveillance System

Enzootic: refers to an endemic animal disease.

FDA: Food and Drug Administration

FSA: Food Standards Agency

HACCP: Hazard Analysis Critical Control Point

Incidence: the number of episodes of a disease occurring over a given period of time in a given group.

Isolate: growth originating from a particular sample.

Jumping Genes: In any bacterial population, there may be a few which are resistant to any particular antibiotic. So when the antibiotic is applied those resistant not only survive, but thrive because they have a selective advantage, however, this is not necessarily the end of the story because the resistance can be transferred to other completely different bacteria. This is because DNA, which contains the genetic code controlling resistance and other inherent characteristics, can transfer from one bacteria to another.

JETACAR: Joint Expert Technical Advisory Committee on Antibiotic Resistance

LVI: Local Veterinary Inspector

MAVIS: Medicines Act Veterinary Information Service: newsletter produced by VMD.

Microflora: the totality of micro-organisms normally associated with a given environment or location.

MRSA: Methicillin-resistant *Staphylococcus aureus*.

Multiple Resistance: resistance to different classes of antibiotics, most frequently due to acquisition of multiple resistance mechanisms (although chromosomally-mediated operons that encode multiple antibiotic resistance have been identified).

NARMS: National Antibiotic Resistance Monitoring System.

NOAH: National Office of Animal Health.

OFT: Office of Fair Trading

OTC: Over the counter

PAHO: Pan American Health Organisation

Phage Typing: a method of distinguishing varieties of bacteria within a particular species on the basis of their susceptibilities to a range of bacteriophages.

PHLS: Public Health Laboratory Service

Prevalence: the number of incidences of a disease at a given time (see also incidence).

RCVS: Royal College of Veterinary Surgeons

RUMA: Responsible Use of Medicines in Agriculture Alliance

Serotype: varieties of bacteria distinguished by their antigenic properties on the basis of their reaction to known antisera.

SMAC: Standing Medical Advisory Committee

Strain: a population of organisms within a species or sub-species distinguished by subtyping.

SVS: State Veterinary Service.

UCS: Union of Concerned Scientists

VMD: Veterinary Medicines Directorate, an Executive Agency of DEFRA.

VPC: Veterinary Products Committee

VRC: Veterinary Residues Committee

VRE: Vancomycin-Resistant Enterococci.

WHO: World Health Organisation

ZAP: Zoonoses Action Plan

Zoonosis: any infectious disease which can be contracted by humans and in which the pathogen is normally maintained within animal populations.

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Finally, if there is any further information that is relevant, please let me know.

Yours sincerely

Verner Wheelock