Antibiotic Use and Antibiotic Resistance in Food Animals in Malaysia: A Threat to Human And Animal Health

Prepared by

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Contents page

Overview

Two tragic events took place recently in Malaysia. The first was reported in the *Borneo Post*, a regional newspaper which revealed that up until August 2013, ten people had died in Sibu Hospital from Carbapenem-Resistant Enterobacteriaceae.[1]

The second tragedy occurred in the first week of October when four people died and 60 others were hospitalised after eating contaminated chicken at a wedding feast in Yan, Kedah. The Health Department said it was most likely due to Salmonella contamination.[2]

These two reports of lethal infections affecting the general public are just the tip of the iceberg. Many more cases are occurring throughout the country, which do not come to public notice. Antimicrobial or antibiotic (both terms will be used interchangeably) resistance (AMR/ABR)* is one of the most serious health threats Malaysia faces. Infections from resistant bacteria are now common and some pathogens have even become resistant to multiple types or classes of antibiotics. With the increasing ineffectiveness of 'drugs of last resort', we are on the brink of a public health disaster/crisis. It is a ticking time bomb in our midst which needs to be taken seriously and urgently dealt with.

AMR is a worldwide problem and governments are beginning to seek coordinated international action to tackle it. In March 2013, the UK's Chief Medical Officer Professor Dame Sally Davies and the Director of the US Centers for Disease Control and Prevention Dr Thomas Frieden warned that antibiotic resistance is a catastrophic threat and a nightmare on par with terrorism and climate change.[3]

The fact that resistant bacteria do not respect national boundaries means that antibiotic use and resulting resistance in one ecological system may have consequences for the resistance situation in another system. Thus antimicrobial resistance in humans and 'non-human' environments are interdependent.

This memorandum looks at the use of antibiotics in food animals in Malaysia; the state of AMR in food animals**that is currently in the public domain in Malaysia; European regulations concerning additives in animal feeds; and some proposals to address the containment of AMR in food animals in Malaysia.

This memorandum examines:

1. Antibiotic use in food animals;
2. Antibiotics as growth promoters;
3. Antibiotic-resistant bacteria in food animals;
4. Use of antimicrobials in livestock in Malaysia;
5. Effects of antibiotics use in food animals on human health;
6. European regulations on antibiotics in animal feeds; and
7. Proposals

*Antimicrobial resistance encompasses resistance to antiviral agents (eg drugs for HIV) and resistance to parasitic agents (eg drugs for malaria). Antibiotic resistance refers to resistance in bacterial agents (eg drugs for tuberculosis and other bacterial infections)

**Food animals essentially refers to animals that are reared for meat consumption.

1. Antibiotic use in food animals

Antibiotic resistance and its spread in veterinary medicine is a worldwide problem. Resistant bacteria carried by food-producing animals can spread to people, mainly via the consumption of inadequately cooked food; handling of raw food or cross-contamination with other foods; but also though the environment (eg animal manure and contaminated water-animal sewage) and through direct animal contact.

The main difference between antibiotic use in humans and animals is that in the latter case, there is mass administration of antibiotics to many animals at the same time for the purposes of disease prevention and growth promotion. A therapeutic dose may be up to 10 – 100 times greater than a dose used in growth promotion. Treatment is directed against a particular infecting microorganism and the goal is to eradicate or control it as quickly as possible. Contagious spread of disease can be fast in large herds. The aim is not very different from a doctor's use of antibiotics to treat humans. But herein lies a significant difference between therapeutic and subtherapeutic use. It is not only the quantity but also the total time of usage that is different.

In the case of growth promotion, smaller doses are administered for longer periods of time, for weeks to months. The net result is that as much as 80% of the total amount of antibiotics given yearly to many food animals goes for growth promotion.#

Such practices provide favourable conditions for the emergence, spread and persistence of antibiotic-resistant bacteria capable of causing infections not only in animals but also in humans.

The antibiotics used for food-producing animals are frequently the same or belong to the same classes as those used in human medicine. Antibiotics are used in greater quantities in healthy food-producing animals than in the treatment of disease in human patients. According to the World Health Organization (WHO), there is no clear evidence of the need for or benefit from the use of antibiotics in animal husbandry.[4]

There are three modes of antimicrobial use in animals ie prophylaxis, treatment and growth promotion. The largest quantities of antibiotics 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 antibiotics. Furthermore a lack of diagnostic services means that most therapeutic antibiotic use in animals is empiric, rather than being based on laboratory-proven disease.[5]

For animals and birds farmed in large herds or flocks, a few ill individuals generally result in the entire herd or flock being treated to avoid rapid contagion and stock losses. In addition, veterinarians in some countries earn as much as 40% or more of their income from the sale of drugs, so there is a disincentive to limit antimicrobial use. [5]

Further, antibiotics that are used as growth promoters are generally not even considered as drugs and are either not licensed or licensed solely as feed additives. Marketing practices of antibiotics for therapeutic, prophylactic or growth promoter uses in animals by industry influence the prescribing patterns and behaviour of veterinarians, feed producers and farmers.

The lack of laws and regulatory mechanisms and poor enforcement regarding the promotion and use of antibiotics in animals and birds are a major contributor to the rampant and indiscriminate use of antibiotics.

2. Antibiotics as growth promoters

Some antimicrobials, especially those that target gram-positive bacteria, are associated with an increase in the rate of animal growth when they are given in subtherapeutic amounts in stock feed to food-producing animals. However these drugs also alter the gut flora of exposed animals such that they frequently contain bacteria that are resistant to the antibiotic used.

When such growth promoters (eg bacitracin, tylosin, spitamycin, virginiamycin, and avoparcin [similar to vancomycin]) belong to a class similar to antibiotics used in human medicine, these resistant bacteria are often also resistant,ie cross-resistant, to important human use antibiotics.

Scientific data strongly suggest that avoparcin use in animals contributes to an increased pool of vancomycin-resistant enterococci (VRE).[5]VRE cause serious infections mostly among immunocompromised patients in hospitals. Such infections are difficult to cure due to the limited number of effective treatment options and are associated with increased morbidity and mortality. There are also concerns that the genes that cause resistance to vancomycin may spread from *enterococci* to other bacteria such as *Staphylococcus aureus*, for which vancomycin is one of the drugs of last resort, leaving few or no treatment options.

3. Antibiotic-resistant bacteria in food animals

Bacteria and resistance to critically important antibiotics associated with food animals include *Escherichia coli* and *Salmonella spp* resistant to 3rd and 4th generation cephalosporins and to fluoroquinolones; *Campylobacter spp* resistant to macrolides and fluoroquinolones; *Staphylococcus aureus* resistant to all beta-lactam-type drugs (ie MRSA); *enterococci* resistant to vancomycin (VRE).[4]

With increasing global trade in food products of animal origin, resistant bacteria spreading from one country to another through food and thereby causing infections are also increasing.

The use of fluoroquinolones (egenrofloxacin) in food animals resulted in the development of ciprofloxacin-resistant *Salmonella*,*Campylobacter* and *E.coli*, which have caused human infections, and spread worldwide through travel and food trade.

Because the same drugs that are used to treat infections in humans are also used for animals, selection of the resistant bacteria has resulted from either type of usage. There is increasing evidence showing that resistant infections in humans to the same bacteria in animals and animal food products. An increasing number of studies indicate that a major proportion of resistant *E.coli* that cause extra-bowel infections in humans may have originated in food animals especially poultry.[4]

If you consider that about 30 times more animals are being given antibiotics yearly than are humans, daily animal fecal excretion can b e 5 – 400 times greater than that of humans. For example, the amount of feces excreted by a cow per day is 100 times more than that of a human. If an animal is given an antibiotic, the fecal bacteria that survive the antibiotic treatment are resistant to it. Therefore, via their excrement, animals are contributing a large amount of resistant bacteria to the natural environment, much larger amounts than are people. The bacteria in this environment move to new areas and new hosts by many routes, through contact with other animals and insects, as well as with food produce.#

Since 2003, a new variant of MRSA has emerged and spread among food animals, primarily in pigs, in many countries. This is already a problem for the control of MRSA in some countries and the prevalence appears to be increasing.[4]

Clostridium difficile (C.difficile) colonises many food animals and also causes diseases in them and has been found in retail meat samples. Since 2005, in the Netherlands and other countries, there has been an increase in community acquired human infections caused by *C.difficile* strain types similar to those found in food animals.[4]

As well as selecting for resistant bacteria, the use of antibiotics in food animals also selects for transferable resistance genes. This raises the possibility that resistance genes could be transferred from animals to humans via non-pathogenic bacteria in food products, and they could then be transferred to bacterial pathogens in the human gastrointestinal tract. Consistent with this hypothesis is the presence of similar vancomycin and cephalosporin resistant genes in both human and animal bacteria.[4]

It is increasingly clear that indiscriminate antibiotic use has become a major public health threat.

Factors associated with the emergence of antibiotic resistance in food-producing animals are similar to those responsible for such resistance in humans. According to WHO, inadequate understanding about and training on appropriate usage guidelines and the effects of inappropriate antibiotic use on resistance are common among farmers, veterinary prescribers and dispensers.[5]

4. Use of antimicrobials in livestock in Malaysia

According to the National Pharmaceutical Control Bureau (NPCB) of the Ministry of Health, Malaysia, there are currently 97 different antimicrobials registered for use. Most of these

Levy, Stuart B, "The Antibiotic Paradox: How the Misuse of Antibiotics Destroys Their Curative Powers', 2nd Edition 2002.

registered drugs are used in poultry and pig farms, less in cattle and goat farms. See Table 1 below for some of the groups of veterinary drugs registered with the NPCB.[6]

Table 1. Registered antimicrobials for use in livestock

Group of Drug	Active Ingredient	Number of Products
B-lactam	Ampicillin, Amoxycillin	8
Cephalosporins	Ceftiofur, Cefadroxil	3
Tetracycline	Chlortetracycline, Oxytetracycline, Doxycycline	13
Sulphonamide	Sulfamethazine, Sulfadiazine, Sulfachloropyrazine, Sulfadimethoxine, Sulfaquinoxaline	8
Macrolide	Tylosine, Erythromycin, Spiramycin, Tylvalosin	10
Aminoglycoside	Neomycin, Gentamicin	2
Fluoroquinolone	Flumequine, Enrofloxacin	8

Some of the drugs listed above fall under WHO's criteria of Critically Important Antimicrobials[7]. These antibiotics identified by WHO are critically important for human health and their use needs to be restricted in the veterinary sector. They include Ampicillin, Amoxycillin, Cefadroxil, Chlortetracycline, Oxytetracycline, Doxycycline, Sulfadiazine, Sulfadimethoxine, Erythromycin, Spiramycin, Neomycin, Gentamicin and Flumequine. Thus more than half of the antibiotics (active ingredient) registered with the Ministry of Health for food animals are not recommended for veterinary use by the WHO.

According to the Department of Veterinary Services (DVS), in Malaysia monitoring of veterinary drug residues/antimicrobials in food of animal origin is based on EEC Directive 1990 and on the capability of the laboratory to conduct the required tests. The Department also states that monitoring of veterinary drug residues in animal feed in Malaysia will be implemented in 2013, in keeping with requirements of the Animal Feed Act 2009.

It appears that the Government of Malaysia has either not kept up with the times or is unaware of the fact that the European Union had instituted a ban on the use of antibiotics as growth promoters in animal feeds in January 2006.

4.1. The certification scheme of the Department of Veterinary Services

The DVSis a gazetted agency under the Ministry of Agriculture Malaysia.The DVS oversees certification programmes, inspections, accreditation and implementation of legislation to supportthe food safety and quality management system in the country. In 2003, the DVS introduced the Livestock Farm Practices Scheme (SALT) on Good Animal Husbandry Practices (GAHP). SALT aims to ensure that farms practising GAHP produce safe and wholesome food of good quality, in sustainable and environmentally friendly conditions. SALT-compliant farms receive a certificate and logo. SALTcertification is awarded to farms that meet the criteria of GAHP, animal health management, bio-security, good infrastructure and prudent use of drugs. The certification scheme coves all types of livestock: beef cattle, dairy cattle, broiler chicken, layer chicken, breeder chicken, deer, goat, sheep and pig.

In 2012, the DVS carried out a preliminary study of antimicrobial resistance in food-producing animals and foods.

- Livestock (chicken): Thirty-eight isolates of different species of Salmonella were taken from chicken cloacal swabs for antimicrobial susceptibility testing. These cloacal swabs were from a SALT supervised and certified farm located in central Malaysia. The study found 13.5% tetracycline-resistant *Salmonella*, 5.4% Polymixin B and Erythromycin-resistant *Salmonella* and 2.7% Chloramphenicol, Penicillin G and Trimethoprim-resistant *Salmonella*.[6]
- Food samples: Forty-three isolates of different species of *Salmonella* was tested from food samples such as beef, mutton and chicken. About 62.8% of *Salmonella* was isolated from imported products (44.2% beef and 18.6% chicken).[6]

Table 2. AMR Salmonella in domestic chicken, imported chicken and imported beef

Food/ Drug	Ampicillin	Chloramphenicol	Ciprofloxacin	Gentamicin	Nalidixic Acid	Streptomycin	Sulphonamide	Tetracycline	Trimethprim	Trimethopim + Sulfamethoxazole
Domestic Chicken	54.5	45.5	9	40	36.4	27.3	63.6	54.5	45.5	36.4
Imported Chicken	87.5	25	25	25	75	50	50	25	37.5	25
Imported Beef	10.5	0	5.3	5.9	10.5	0	5.3	15.8	10.5	0

Source: Hamid, AkmaNgah 2012. Country Report: Malaysia, presented at FAO International Workshop on the Use of Antimicrobials in Livestock Production and Antimicrobials Resistance in the Asia Pacific Region, 22 – 23 October 2012, Negombo, Sri Lanka.

It is clear from this preliminary DVS study that there are problems with the SALT certification scheme. More than half of the domestic chickens harvested from the SALT certified farm in this study were found to be resistant to ampicillin, sulphonamide and tetracycline. The situation was even worse with imported chicken: the study found that 87.5% of bacteria were ampicillin-resistant, 75% were Nalidixic Acid-resistant and 50% were Streptomycin and Sulphonamide-resistant.

These findings have grave implications for public health. Antibiotics which are purportedly life-saving drugs for the treatment of many human infections have become ineffective or useless by virtue of the fact that food animals harbour these antibiotic resistant bacteria. Since the same antibiotics that are used for treating people are also used in animal feeds and to treat livestock, these drugs may not be effective in the treatment of human infections.

The DVS study also has implications for cross-resistance. There are indications that resistance has spread across several classes of drugs. This essentially means that if a person becomes ill, doctors will either have fewer drug options for his/her treatment or treatments with more expensive drugs will have to be instituted.

5. Effects of antibiotics use in food animals on human health

i. There is broad scientific consensus on detrimental effects on human health associated with the use of antibiotics in food animals. Some examples of documented detrimental effects by country include:

5.1. Malaysia

Researchers in Malaysia recently revealed the presence of multidrug-resistant strains of *Listeria monocytogenes* in frozen burger patties taken from supermarkets and other retail shops in the country.[8] Commonly found in raw foods, *L. monocytogenes* can causelisteriosis, common symptoms of which range from gastrointestinal upset to headaches, fever and in severe cases, brain infection and/or blood poisoning. The study examined the susceptibility of *L. monocytogenes* isolated from raw beef, chicken and vegetarian patties to 11 different antibiotics. Thirteen out of 41 bacteria samples or isolates were not resistant to any of the antibiotics, while 28 were resistant to at least one and 19 were resistant to at least two antibiotics. Tetracycline followed by erythromycin resistance were the most common forms of resistance.

5.2.. China

Researchers in China also demonstrate antibiotic resistance due to intensive use of antibiotics in animal feeds. Manure that was processed for disposal was assessed for concentrations and types of antibiotic resistance genes (ARGs).The study found that antibiotics and heavy metals used as feed supplements were elevated in the manure, suggesting the potential for coselection of resistance traits. According to the researchers, diverse, abundant, and potentially mobile ARGs in farm samples suggest that unmonitored use of antibiotics and metals is the cause for the emergence and release of ARGs to the environment.[9] A study carried out in the US lends further support to the thesis that stored swine manure and faeces are reservoirs for ARGs.[10]

5.3. Europe

A 2003 study carried out in Europe found evidence that the antibiotic avoparcin used as a growth promoter in food animals resulted in the development and amplification of vancomycin-resistant enterococci (VRE) and subsequent colonisation of a significant percentage of the human population up the food chain.[11] A subsequent ban on the use of avoparcin in food animals in the EU resulted in a marked reduction of the percentage of the general population carrying VRE in their bowels.This study went on to further point out that the use of ciprofloxacin in food production in many countries has resulted in the development of ciprofloxacin-resistant strains of *Salmonella spp.* and *Campylobacter spp.*, which subsequently have caused human infections.

A 1998 study found that use of animal feed supplemented with the antibiotic tylosinhas led to the development of erythromycin-resistant streptococci and staphylococci in both animals and their human handlers.[12]

5.4. Portugal

A more recent study carried out by Novais C *et al* in six pig farm environments in Portugal found *Enterococcus* isolates from a variety of samples in the pigs, feed/medicines/antiseptics and pig farm facilities, most using antibiotics. *Enterococcus* isolates resistant to antibiotics were recovered from samples of different origin (swine, feed/antiseptics, animal residues and pig farm facilities). The study showed that *E. faecium* was more frequently resistant to ampicillin, ciprofloxacin or nitrofurantoin and *E. faecalis* to tetracyclines, chloramphenicol or aminoglycosides.The study also proved that there was transfer of resistance to several antibiotics, including vancomycin and ampicillin.The study suggested that pig farm environments have the underestimated potential role of being transmission agents of multidrug-resistant (MDR)*Enterococcus* to animals and, possibly, to humans.Of particular concern was the fact that continuous contact of swine with MDR *Enterococcus* by different routes (e.g. feed, dust, air and rooms) might decrease the impact of restrictive antibiotic use policies. The study concluded that there was a clear need to reinforce different interventions at the husbandry management level.[13]

ii. While it is acknowledged that the main contributor to rising antimicrobial resistance in human medicine is the overuse and misuse of antimicrobials by doctors, other health professionals and patients, there is now sufficient and increasing supporting evidence linking newly-emerging resistant bacteria in animals being transmitted to humans mainly through meat and other food of animal origin or through direct contact with farm animals. Food-borne pathogenic bacteria such as *Salmonella* and *Campylobacter* and the normally harmless (in healthy persons and animals) *Enterococcus* have become resistant to classic treatment in humans as a consequence of the use of certain antimicrobials in agriculture.[14]

5.5. Campylobacter

Following the introduction of fluoroquinolones for use in poultry there has been a dramatic rise in the prevalence of fluoroquinolone-resistant *Campylobacter jejuni* isolated in live poultry, poultry meat and from infected humans. Prior to any use in poultry, no resistant strains were reported in individuals with no previous exposure to quinolones[5]. Because of their broad antibacterial spectrum, fluoroquinolones are often used for treatment of gastrointestinal infections in severely ill or immunocompromised patients. Fluoroquinolone-resistant *C.jejuni* has been associated with therapeutic failures in humans.[16]

A 2001 US Food and Drug Administration study states that since fluoroquinolones were approved for use in food-producing animals, there have been reports of links between fluoroquinolones for therapeutic use in food-producing animals and the development of fluoroquinolone resistance in *Campylobacter* in animals and humans. The approval of these drugs in food-producing animals in the Netherlands, Spain and the US preceded increases in resistance in *Campylobacter* isolates from treated animals and ill humans. A 1999 study published in the *New England Journal of Medicine* lends support to this link. The study showed that resistance of human *Campylobacter jejuni* infections to quinolones increased from 1% in 1992 to 10% in 1998.Resistant infections that were domestically acquired in the

US increased significantly from 1996 through 1998. This finding was associated with the licensing of fluoroquinolones for use in poultry in 1995.

A recent study[15] to determine the occurrence of *Campylobacter spp* in live chickens sold at wet markets in the state of Selangor, Malaysia, found multidrug resistance in the isolates of cloacal swabs taken from the chickens. Of the 90 chickens examined, 68 (75.6%) were positive for *Campylobacter*. *Campylobacter* were recovered from caecal swabs (53/90) and cloacal swabs (34/90) and *Campylobacter coli* (46 isolates) were identified slightly more than *Campylobacter jejuni* (41 isolates), but these differences were not significant ($p<0.05$). The most frequently observed resistance was to cephalothin (95.5%), followed by tetracycline (80.8%), erythromycin (51.4%), enrofloxacin (42.4%) and gentamicin (24.4%). Multidrug resistance (resistant to three or more antibiotics) was detected in 35.3% isolates. *Campylobacter jejuni* showed nine resistance profiles and the most common was to gentamicin-eryhtromycin-enrofloxacin-cephalothin-tetracycline (32.4%) combination while *C. coli* showed six profiles, with cephalothin-tetracycline (32.2%) combination being most common.

5.6. Salmonella

Antibiotic use in animals selects for resistance among non-typhoidal *Salmonella spp.* Antibiotic resistance limits the therapeutic options available to veterinarians and physicians for the subset of clinical cases of nontyphoid *Salmonella* which require treatment. A recent example is a clone of *S.typhimurium DT104* resistant to ampicillin, tetracycline, streptomycin, chloramphenicol and sulphonamides which has become prevalent in many countries including the UK, Germany and the US[5].

The sentinel case in the US was of a 12-year-old child from Nebraska who acquired ceftriaxone-resistant *Salmonella*.According to a study reported in 2000 in the *New England Journal of Medicine*, the child lived on a farm and his father was a veterinarian who had been treating several cattle herds for outbreaks of *Salmonella* infection.Ceftriaxoneresistance emerged in the cattle herds, probably following use of the antibiotic ceftiofur or other antibiotics that would have selected for and maintained the ceftriaxonedeterminant within the intestinal flora of the involved herds, and then spread to the child via the father.

Following the introduction of fluoroquinolones for use in food-producing animals, the emergence of *Salmonella* serotypes with reduced susceptibility to fluoroquinolones in humans has become a cause for particular concern. This has been substantiated by a recent outbreak of quinolone-resistant *S.typhimunium DT104* resulting in treatment failures in hospital patients in Denmark[5].

5.7. Escherichia coli

Multi-resistant *Escherichia coli* have been selected by the use of broad-spectrum antimicrobials in both livestock and humans. The development of antibiotic resistance in *E.coli* creates problems due to their high propensity to spread antimicrobial resistance genes.

Resistance genes have been traced from *E.coli*in animals to *E.coli* in humans. Certain *E.coli* are foodborne pathogens and most of these strains are currently susceptible to antibiotics.[16] Should therapy be required, it could be compromised by the development of resistance in these strains.

In the Netherlands the same genes encoding for ESBL (extended spectrum beta-lactamases) in *E.coli* isolates are found in both food animal isolates (especially poultry) and in those causing serious infections in people.[7] ESBLs are enzymes that can be produced by bacteria making them resistant to penicillin and cephalosporins.

Antibiotic-resistant bacteria isolated from humans resulting from the use of antibiotics in food animals have human health consequences. They include:

- Infections that would not otherwise have occurred.
- Increased frequency of treatment failures and increased severity of infection.
- Increased severity of infection includes prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalisation and increased mortality.

Antibiotic resistant strains in food products in Malaysia

In summary:

- local chickens tested by the DVS were positive for *Salmonella* resistant to tetracycline, Polymixin B, Erythromycin, Chloramphenicol, Penicillin G and Trimethoprim while imported chicken tested positive for *Salmonella*. Beef, mutton and chicken samples all harboured antibiotic resistant *Salmonella*.
- Live chickens sold at wet markets in Selangor tested positive for *Campylobacter.* Most frequently observed resistance was to cephalothin, tetracycline, erythromycin, enrofloxacon and gentamicin. More than a third of bacteria samples showed multidrug resistance.
- Frozen burger patties taken from supermarkets and retail shops showed the presence of multidrug-resistant strains of *Listeria monocytogenes*; the most common forms of resistance involved tetracycline followed by erythromycin.

It is clear from the above that the safety of meat products in Malaysia is in doubt, antibiotics are becoming ineffective/useless and the health and well-being of consumers are at stake. DVS and local studies have clearly shown: that antibiotic resistant bacteria are present in the food products in the country, that antibiotics are increasingly powerless against them and which meat products harbour these antibiotic resistant bacteria.

5.8 Antibiotic resistance in Malaysian hospitals

Institute for Medical Research (IMR) data collected from 37 hospitals throughout Malaysia for the National Surveillance of Antibiotic Resistance for 2012 found that:

- For gram- negative bacilli like *Escheria coli* the rate of resistance to 3rd and 4th generation cephalosporins had increased in 2012 compared to 2011 respectively for Cefotaxime (20.2%:15.8%), Ceftazidime (14.8%:11.7%) and Cefoperazone/Sulbactam (2.5%:1.8%). *E.coli* also showed increased resistance to one fluroquinolone - Ciprofloxacin (23%:21.2); Ampicillin (69.1%:67.1%) and ampicillin/sulbactam (24.5%:22.1%); gentamicin (12.3%:11.8%) and piperacillin/tazobactam (3.1%:2.6%).

- *Salmonella* showed a slight increase in resistance rates towards cephalosporins ie. ceftazidine and ceftriaxone. In the gram-positive cocci category the overall rate of MRSA was 17.3% although the rate in hospitals varied from 2.3% to 25.8%.

- For Group B *Streptococcus*, resistance to erythromycin, clindamycin, tetracycline and co-trimoxazolehas increased in 2012 compared to 2011. The vancomycin resistance rate for *Enterococcus faecium* has increased to 8.7% in 2012 compared to 5.4% in 2011.[17]

Clearly the increase in antibiotic resistant infections in Malaysian hospitals has multiple causes including inappropriate use of antimicrobial medicines, including in animal husbandry, poor infection prevention and control practices, and insufficient diagnostic, prevention and therapeutic tools. Underlying factors that accelerate the emergence and spread of antimicrobial resistance include the lack of a comprehensive and coordinated response as well as weak or absent antimicrobial resistance surveillance and monitoring systems.

It must be stressed that in view of the link between antibiotic use in food-producing animals and the occurrence of antibiotic-resistant infections in humans, the increase in antibiotic-resistant infections in Malaysian hospitals must be taken very seriously.

6. European regulations on antibiotics in animal feeds

The European Council's (EC) basis for harmonising regulations on feed additives was so that a common market for animal feeds could be established. The EC was able to do that with the enactment of Council Directive 70/524 on December 14, 1970. Prior to this, national regulations of individual member states differed with regard to basic principles. This Directive was later replaced with Council Regulation 1831/2003, which is the Directive currently in force.Regulation 1831/2003 stated that antibiotics, other than coccidiostats and histomonostats, might be marketed and used as feed additives only until December 31, 2005. Anticoccidial substances, such as antibiotics ionophores, also will be prohibited as feed additives before 2013.[18]

In 1969, the Swann Committee, established by the British Government, issued a report calling for restricted use of antibiotic growth promoters (AGPs) to reduce the risk of resistance developing to drugs used in human medicine. The committee was formed in response to discovery of transferable oxytetracycline resistance from food animals to *Salmonella enteric Serovar Typhimurium*. Its recommendations led to the withdrawal of penicillin, streptomycin, and tetracyclines from the list of authorised AGPs in many European countries in 1972-1974.[19]

Sweden prohibited the use of antibiotics in foodstuffs in 1986. Swedish farmers requested that ban in part because a 1984 report stated that consumer confidence in meat safety dropped after learning that 30 tons per year of antibiotics were being used in Sweden in food animal production. Following this, other European Union (EU) member states that prohibited the use of some antibiotics in animal feeds included: Denmark, which banned avoparcinon May 20, 1995, and Germany, on January 19, 1996, arguing that this glycopeptide antibiotic produced resistance to glycopeptides used in human medicine. Spiramycin was prohibited in Finland on January 1, 1998 because this product was used in human medicine, while Denmark also prohibited virginiamycin on January 15, 1998, also based on the argument that streptogramins were clinically important in human medicine.

Also in the early 1990s, vancomycin-resistant *Enterococcus* (VRE) was detected among patients in Europe. In the search for a community reservoir of that resistance, VRE was found in meat and also in manureon farms where avorparcin was used as a growth promoter. In 1997, the EU banned avorparcin for all uses in agriculture. In 1999, EU discontinued the further use of AGPs from drug classes also used in human medicine, imposing a ban on tylosin, spiramycin, virginiamycin and bacitracin.

In 1999, the EU backed a ban on penicillin and other antibiotics used to stimulate growth in farm animals.Within four years, antibiotic use in animals dropped36% in Denmark,45% in Norway and 69% in Sweden.[20]

On January 1, 2006 an EU-wide ban on the use of antibiotics as growth promoters took effect. As a result, the last four antibiotics which had been permitted as feed additives to help fatten livestock were disallowed to be marketed or used from that date. The ban was the final step in the phasing out of antibiotics used for non-medicinal purposes.

After 2013, medical substances in animal feeds in the EC will be limited to therapeutic use by veterinary prescription only.

6.1. Why the EU banned antibiotics as growth promoters in animal feeds

The goal of the EU and country-specific bans on non-essential antibiotic use in food animal production is to reduce the pool of resistance genes in farm animals and other non-human settings. Although a resistance monitoring system was not in place in 1986 when the first European ban took effect in Sweden, the agriculture extension services, efforts to educate farmers and a system for monitoring antimicrobial use were in place to support the ban.

After the ban, antimicrobial consumption fell in that country without a loss in meat production.[19]

In Denmark, DANMAP data demonstrate that the same ban on non-essential antibiotic use in food animal production is working without major consequences for animal health. The Danish approach includes extensive monitoring systems to track drug resistance and antimicrobial use as well as services for research and analysis.

Dutch efforts on establishing a monitoring system differ from those in Sweden, Denmark and the UK. Although Dutch officials promulgated regulations to limit antibiotic usage in animal production, they did so without a plan to implement or enforce them. So, when the AGP ban went into effect, food animal producers were not ready to alter their practices.Subsequently, when the Netherlands experienced high levels of antibiotic resistance in food animals following massive use of these agents, the government intervened by mandating a 50% reduction in antibiotic usage in the next three years through defined daily dosages and transparency in prescriptions.

The EU ban on antimicrobials as growth promoters was based on direct evidence from several studies[19] linking use of AGPs in farm animals with the emergence, spread and transfer of resistance genes from microorganisms associated with those animals to bacterial pathogens that infect humans. These studies established three important principles:

- Low-dose, nontherapeutic use of antibiotics selects for resistance to those antibiotics
- Resistance to antibiotics used in humans is determined by the same mechanism as those used in animals.
- Resistance genes disseminate via the food chain into the intestinal flora of humans.

6.2. Effects of the ban

The EC's main reason for instituting a ban on the use of antibiotics as growth promoters was to deflect the risk of transferring antibiotic resistance genes to humans.

- Available data suggest that the growth-promoter ban has driven an increase in infections and therefore a substantial increase in the use of therapeutic antibiotics for food animals in Europe, but the ban also has reduced overall antibiotic use in animals. Reports show that in Sweden, as a result of the ban and a focus on disease prevention and correct use of antimicrobials, the total use of antibacterial drugs to animals decreased by approximately 55% in the period 1986 - 1999, and a relatively low prevalence of antimicrobial resistance has been maintained.[18]
- The ban on growth promoters actually creates a demand for the improvement of farm hygiene.According to WHO, under good production conditions, it is possible to reach good and competitive production results for the rearing of poultry without the continuous use of antibiotics in feeds. Studies on alternative and safer non-antimicrobial substances have produced positive results.These alternatives include enzymes, prebiotics and probiotics, or acidificationof diets.[18]

- The ban on antibiotics in animal feeds will have consequences in the international trade of poultry meat because the EU only imports foods obtained from animals that were not fed with antibiotics in application of the precautionary principle allowed by the World Trade Organization.[18]

Conclusion

It is established that antimicrobial resistance is influenced by both human and non-human antimicrobial usage. It is also acknowledged that antimicrobial resistance is a global public health problem; the global health community is already beginning to speak of a post-antibiotic era. The latest in the chorus list of naysayers against antibiotics in animal feeds is the Ontario Medical Association in Canada. Its report recommends the setting up of a system to track who is buying antibiotics in the farming industry and how much is being bought; the setting up of an independent body to develop and maintain best antibiotic use guidelines that Ontario doctors can use to guide their practice when confronted with resistant bacteria and less familiar antibiotics; instituting a veterinary prescription-only standard of antibiotic access for livestock and closing the loop which allows farmers to import antibiotics for own use, and amending the Food and Drugs Act.[21]

The state of antimicrobial resistance in Malaysia is not known and results of existing research in this area have not been made public. Comparatively little published information exists on antibiotic usage in animal husbandry in the country.

There are clear indications that some SALT certified farms are unable to meet Good Animal Husbandry Practices. It is unclear if the causes are lapses in hygiene standards, imprudent use of drugs or lack of the required infrastructure. The fact that imported meat products have shown higher percentages of resistant strains of *Salmonella* points to lapses in monitoring and enforcement.

7. Proposals

In view of the above and in response to the serious global and national AMR problem, the Consumers' Association of Penang (CAP) urges the Ministries of Health and Agriculture to:

7.1 Ban antibiotic use in animal feeds in light of the EU ban on antibiotics in animal feed. In order to institute a similar ban it may be worthwhile to examine the experiences of Sweden, Denmark, Netherlands and the UK (see Annex 1);

7.2. Beef up resources and expertise to:

7.2.1. Create a national system to monitor antibiotic use in food animals. This includes actions to improve and refine the collection of data on antibiotic use in the country. Quantities and classes of antibiotics used in food animals according to animal species need to be documented. This is necessary for risk analysis, interpreting resistance surveillance data and to assess the impact of interventions to promote prudent use;

7.2.2. Monitor resistance and track changes in antibiotic resistance through on going surveillance at local, state and national levels. This will identify emerging health problems so that timely corrective action to protect human health is taken;

7.2.3. Share local, state and national information and data on AMR and emerging issues in human and animal health. To devise early warning systems to trigger appropriate containment measures to limit the spread of resistant organisms. Infections do not respect borders;

7.2.4. Conduct research to better understanding the significance of different transmission pathways between the environment, humans, animals, and the food supply chain in promoting transfer or increase of resistance in human and veterinary pathogens. This will aid in targeting and prioritising interventions to minimise resistance;

7.2.5. The containment of antibiotic resistance must be made a national priority. The National Surveillance of Antibiotic Resistance Programme under the Ministry of Health cannot work alone. There is a need to create a national intersectoral body or task force comprising healthcare professionals, veterinarians, academics, agricultural scientists, consumers, the media, to raise awareness about AMR, prioritise research, collect data, recommend policy measures to contain AMR eg formulating principles for a new Animal Health Law;

7.2.6. Introduce and or enforce laws on the use of antibiotics in animals ie approval of veterinary drugs and restrictions on their use; promote animal health; strengthen hygiene in the food chain;

7.2.7. Introduce and strengthen laws on prescriptions for all antibiotics used for disease control in food animals;

7.2.8. Reduce the use of specific classes of antibiotics especially those used in human health. WHO has classified 3^{rd} and 4^{th} generation cephalosporins and fluoroquinolones as critically important antibiotics for humans. Prohibit for animal use any new drug developed for human medicine and of those that are used only in human health;

7.2.9. Improve animal health to reduce the need of antibiotics through measures like immunisation against prevalent infections. In 1987 Norway introduced effective vaccines in farmed salmon and trout and improved health management which reduced the annual use of antibiotics in farmed fish by 98% between 1987 and 2004. Many countries and the EU have regulations to enforce and promote vaccinations as a method of reducing infections in food animals;

7.2.10. Develop guidelines for veterinarians to reduce the overuse and misuse of antibiotics in food animals;

7.2.11. Provide education and training for livestock farmers on responsible use of antibiotics;

7.2.12. Introduce AMR issues and strategies for containing resistance in veterinary science courses;

7.2.13. Encourage good farming practices and best practices in disease control eg appropriate housing design for animals, good disinfection procedures, isolation of sick animals, use of vaccines and disease eradication programmes;

7.2.14. Actively engage farmers to ensure information and guidelines are effectively disseminated;

7.2.15. Monitor imported meat products for antibiotic resistant contamination and the stringent enforcement of rules;

7.2.16. Improve hygiene in food production and processing to reduce contamination. The FAO/WHO Codex Alimentarius provides recommendations for many aspects of food production including hygiene from primary production through to final consumption, highlighting key controls at each stage. It recommends a *Hazard Analysis and CriticalPoint* (HACP) approach;

7.2.17. Monitor the extent of illness caused by food borne contamination and identify the sources of infection as part of prevention efforts;

7.2.18. Identify foods local and imported responsible for outbreaks of *Salmonella* infections and other food borne contamination;

7.2.19. Monitor the spread of *Salmonella* among animals on farms to prevent their spread. In 2006 the EU put in place a programme with specific targets for reduction in *Salmonella* contamination. By 2009, 18 states had reached the EU reduction targets in breeding flocks of fowl and saw a decreasing trend in human salmonellosis cases;

7.2.20. Conduct public education on issues related to antibiotics use in food animals to raise awareness of the dangers to health and unclear benefit from their use in agriculture and aquaculture;

7.2.21. Educate consumers and food workers about safe food handling practices and how to avoid *Salmonella* infections;

7.2.22. Develop and strengthen international collaboration with international bodies to improve knowledge and understanding of AMR, prudent use of antibiotics, development of diagnostics etc. There are several international networks which coordinate AMR surveillance in human and animal populations. The Global Foodborne Infections Network (GFN) for foodborne pathogens like *Salmonella* and *Campylobacter spp*; the Pan American Health Organisation (PAHO); the European Antimicrobial Resistance Surveillance Network (EARS-Net); and the international molecular subtyping network for foodborne disease surveillance (PulseNet International) are some examples.The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) has developed guidance documents for global standardisation of methods for monitoring AMR and antibiotics use in food animals; and

7.2.23. Demonstrate leadership to build political support for action at the regional level through ASEAN to develop and strengthen multilateral and bilateral commitments for the prevention and control of AMR in all sectors.

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Annex 1

Country –Specific Experiences and Perspectives

Sweden

Sweden established SVARM to monitor antimicrobial resistance in farm animals in 2000, although Swedish officials first collected statistics on antimicrobial use in agriculture as early as 1980. After the 1986 ban, sales of antibiotics for animals fell from an average of 45 tons of active substance to about 15 tons by 2009.

To facilitate the move to a new mode of animal husbandry, Swedish officials developed guidelines on feed, medication, management, and hygiene to keep animals healthy and prevent infections. Large efforts were directed to problem-oriented research and to providing extension services for farmers. Early problems following the ban included necrotic enteritis and Clostridium perfringens-associated diarrhea in poultry and weaning diarrhea and dysentery in piglets and slaughter pigs, respectively.

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Denmark

In 1995, Denmark established DANMAP, a system for monitoring antibiotic resistance in farm animals, to follow the impact of withdrawing antibiotic growth promoters (AGPs). Comparable monitoring of antibiotic resistance in humans began three years later. The Danes withdrew AGPs from food animal production to reduce an observed reservoir of antibiotic resistance in food animals. Avoparcin use was banned in 1995 and virginiamycin in 1998, with a comprehensive ban on AGPs by 2000. Danish swine and poultry production continues to thrive following the ban. Meanwhile, Denmark has experienced major reductions in antimicrobial consumption and resistance.

Between 1992 and 2008, Danish farmers increased swine production by 47%, maintaining their standing as being among the largest exporters of pork in the world while exporting 90% of pork they produce. During this period, antimicrobial use in swine was reduced by 51%, from 100.4 to 48.9 mg/kg meat. Since the ban, production in poultry has increased slightly, and there has been a 90% reduction in total antimicrobial usage: from about 5,000 kg used in 1995 to less than 500kg used (for therapy) in 2008.

Following the ban on AGPs, therapeutic use of antimicrobials gradually increased following outbreaks of Lawsoniaintracellularis and post-weaning multisystemic wasting syndrome

(PMWS) in pigs. However, the overall use of macrolides, which the World Health Organization (WHO) classifies as critically important for human medicine, was reduced.

From 1996 – 2008, there were major reductions in vancomycin-resistant E. faecium from broilers and pigs following decreased use of avoparcin. Similarly, macrolide resistance (tylosin is used for therapy as well as AGP) and avilomycin resistance were reduced in E. Faecium among broilers.

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The Netherlands

Dutch officials established MARAN, a system for monitoring antibiotic resistance in food pathogens, animal pathogens, and indicator organisms in 1999. Dutch sales data indicate that with the termination of growth promoters in 2006, therapeutic drug usage increased to levels that kept total antibiotic use static, highlighting the importance of clearly defining "therapeutic' and "non-therapeutic" use. In 2007, 90% of the 600 tons of antibiotics was administered through oral mass medication.

Despite the ban of AGPs, nothing changed in the Dutch food animal production system. Antibiotics were still used extensively to treat infectious diseases, to balance feed quality in broilers, and to treat non-infectious conditions such as dysbacteriosis. Factors contributing to this scaled-up use of antibiotics included farm expansions, poor use of infection control measures, insufficient government control over antibiotic use and sales, and resistance from farmers to mandated changes in their practices.

Nonetheless, the withdrawal of AGPs led to a decrease of VRE in food animals and a decrease in resistance to avilamycin. However, use of high levels of antibiotic continues, while multidrug-resistant bacteria continue to spread among food animals. For example, throughout Dutch farms, there is a high prevalence of fluoroquinolone-resistant Campylobacter in poultry, MRSA ST398 in pigs and veal calves, and ESBL-producing E.coli and Salmonella in broilers, according to a 2008 report from MARAN. The occurrence of methicillin-resistant Staphylococcus aureus and extended-spectrum β-lactamase-producing bacteria among food producing animals has implications for public health in the Netherlands and affects costs in health care settings.

The Dutch experience illustrates that withdrawing AGPs needs to be accompanied by other interventions, including appropriate monitoring and disease control measures in the agricultural sector. Without such measures, bans on AGPs will be replaced by increased therapeutic use of antimicrobials. The Netherlands has responded to its antibiotic resistance crisis with a mandate to reduce their use in food animals by 50% during the next three years and to establish a registration process for veterinary prescription of antibiotics.

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Most UK poultry and many swine producers stopped using AGPs before the EU ban in 2006. A government ministry organizedstakeholder meeting provided general support for farmers as they implemented the ban, and also furnished them with relevant reports from Denmark and the WHO. Pharmaceutical companies also informedfarmers about alternative approaches to cope with the move away from AGP use on farms and the news media invited several farmers to be interviewed; those reports helped inspreading the word about the move from AGPs to alternative strategies for food animal production.

Officials collected antibiotic sales data from pharmaceutical companies indicating an overall decline in AGP usage from 1998 onwards. In addition, following the ban, total consumption of therapeutic antimicrobials declined in food-producing animals. However, therapeutic use of macrolides increased, possibly to control organisms such as Lawsoniaintracellularis. Although UK data are incomplete, necrotic enteritis in broilers remained under control, whereas proliferative haemorrhagic enteropathy in pigs and cholangeo-hepatitis in broilers increased after withdrawal of AGPs.

In the absence of a detailed study, two abattoir surveys of antibiotic use in pigs following the ban on AGPs indicate that resistance to erythromycin in Campylobacter coli and Enterococcus faecium declined from 85% in 1999-2000 to 36% in 2007. Vancomycin resistance in E. faecium from pigs was less than 1% in both surveys.

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Source: Cogliani C, Goossens H, Greko C. 2011. Restricting Antimicrobial Use in Food Animals: Lessons from Europe. Microbe 2011, vol. 6, no. 6: 274-279.