Control and monitoring of antimicrobial resistance in bacteria in food-producing animals in Japan

Katsuaki Sugiura[(1)], Tetsuo Asai[(2)], Masami Takagi[(1)] & Takashi Onodera[(3)]

Summary

Increased antimicrobial resistance in bacteria that cause infections in humans is a threat to public health. The use of antimicrobials in food-producing animals in the form of veterinary medicine and feed additives may lead to the emergence or spread of antimicrobial resistance in bacteria of animal origin. In Japan, the use of antimicrobials in food-producing animals is regulated by the Pharmaceutical Affairs Law and Feed Safety Law to minimise the risk of emergence and spread of antimicrobial resistance in bacteria. Since December 2003, all antimicrobials used in food-producing animals have been subjected to risk assessment by the Food Safety Commission. In addition, an antimicrobial resistance monitoring programme has been in place since 2000 to monitor the evolution of resistance to different antimicrobials in bacteria in food-producing animals.

Keywords

Additive, Animal, Antimicrobial, Feed, Food, Japan, Monitoring, Public health, Resistance, Veterinary.

Controllo e monitoraggio della resistenza antimicrobica dei batteri negli animali da produzione alimentare in Giappone

Riassunto

L'aumento della resistenza antimicrobica dei batteri che provocano infezioni nell'uomo costituisce una minaccia per la salute pubblica. L'impiego di antimicrobici negli animali da produzione alimentare sotto forma di medicinali veterinari e additivi per mangimi può portare all'insorgenza o alla diffusione di resistenza antimicrobica nei batteri di origine animale. In Giappone, l'impiego di antimicrobici negli animali da produzione alimentare è regolamentato da due leggi ("Pharmaceutical Affairs Law" e "Feed Safety Law") al fine di minimizzare il rischio di insorgenza e diffusione di resistenza antimicrobica nei batteri. Da dicembre 2003 tutti gli antimicrobici utilizzati per gli animali da produzione alimentare vengono sottoposti a una valutazione del rischio da parte della Food Safety Commission. Inoltre, dal 2000 è attivo uno specifico programma di monitoraggio per controllare l'evoluzione della resistenza batterica a differenti antimicrobici negli animali da produzione alimentare.

Parole chiave

Additivo, Animale, Antimicrobico, Cibo, Giappone, Mangime, Monitoraggio, Resistenza, Salute pubblica, Veterinario.

(1) Food and Agricultural Materials Inspection Centre, 2-1 Shintoshin, Chuo-ku, Saitama, Saitama 330-9731, Japan
katsuaki_sugiura@nm.famic.go.jp
(2) National Veterinary Assay Laboratory, 1-15-1, Tokura, Kokubunji, Tokyo 185-8511, Japan
(3) Department of Molecular Immunology, University of Tokyo, Bunkyo-ku, Tokyo 113-8657, Japan

Introduction

Increased antimicrobial resistance in bacteria that cause infections in humans is a threat to public health. Any use of antimicrobials, be it in humans, animals, plants or food processing, can lead to bacterial resistance.

Antimicrobials are used in human medicines, veterinary medicines, agriculture and aquaculture in Japan, and obviously in many other developed countries. They are subject to manufacturing and marketing authorisation in accordance with the Pharmaceutical Law, Feed Safety Law and Agricultural Chemicals Regulation Law, depending on the purposes for which they are used. Quantities of antimicrobials marketed in Japan under the respective laws are shown in Figure 1. The annual amount of antimicrobials used in human medicines and veterinary medicines is 500 and 1 000 metric tons, respectively. A total of 200 metric tons are used as feed additives and 400 metric tons as agricultural chemicals.

Concern has been expressed in regard to the use of antimicrobials in animal production which may lead to selection for resistant bacteria that may spread to humans through consumption of food of animal origin, reducing or nullifying the therapeutic effect of antimicrobials in medicines.

This paper outlines the measures taken in livestock production in Japan to control the emergence and spread of antimicrobial resistance as well as the results of the Japanese Veterinary Antimicrobials Resistance Monitoring (JVARM), an antimicrobial resistance monitoring programme.

Control of antimicrobial resistance in bacteria in food-producing animals

In Japan, some antimicrobials that have a growth promoting effect are approved as feed additives by the Minister of Agriculture, Forestry and Fisheries in accordance with the Law on the Assurance of Safety and Improvement of Feed Quality (Law No. 35, 1953) (Feed Safety Law), and used in feed for the purposes of promotion of the efficient use of feed nutrient ingredients. Antimicrobials used for therapeutic purposes are subject to regulation by the Pharmaceutical Affairs Law and are permitted for use only when prescribed by medical doctors or veterinarians.

Antimicrobial feed additives

Antimicrobials added to feed for growth promoting purposes are classified as feed additives and subject to regulations of the Feed Safety Law. Based on this Law, only feed additives approved by the Minister of Agriculture, Forestry and Fisheries are authorised for use in feed.

The approval of feed additives is made in consultation with the Agricultural Production

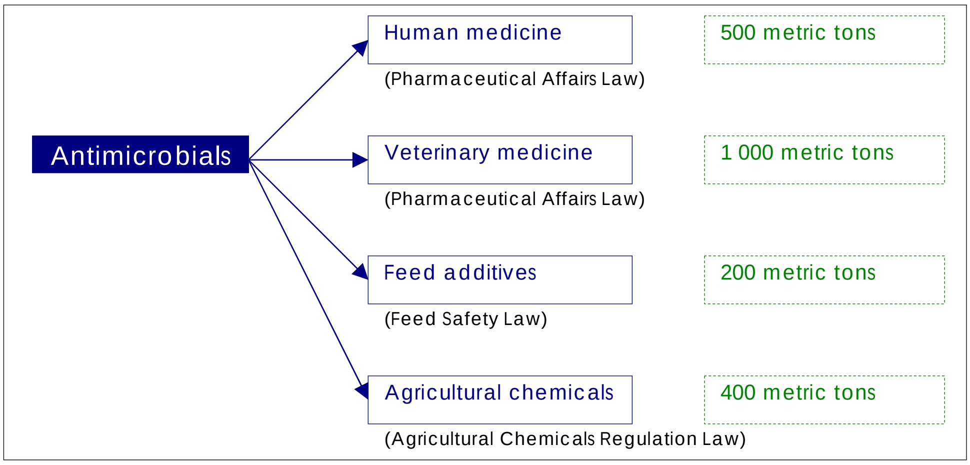

Figure 1
Approximate annual amounts of antimicrobials used for different purposes in Japan
In brackets are the laws that regulate the use of antimicrobials for the purposes indicated

Materials Council. They are examined for toxicity, safety in target animals, risk of emergence of bacterial resistance and residual nature in the final animal products produced. They are also subject to risk assessment by the Food Safety Commission prior to approval. Antimicrobials that are not eliminated from animals within seven days after application are not approved. Feed containing antimicrobial feed additives must conform to various standards and specifications set by the Minister of Agriculture, Forestry and Fisheries. In accordance with these standards and specifications:

- the use of non-approved feed additives in feed is prohibited
- feed additives are permitted for use in feed for the specified target animals at a specified amount
- a maximum of four antimicrobials are allowed to be added to feed
- the addition to feed of two or more antimicrobials of the same family is prohibited
- the use of feed additives for seven days prior to the shipment of animals is prohibited
- packages of feed containing feed additives must be labelled with the name and amount of antimicrobial feed additives added.

In addition to these standards, the marketing of antimicrobial feed additives is prohibited unless they have been tested by the Food and Agricultural Materials Inspection Centre (FAMIC) or they are produced by manufacturers that have received approval from the Minister of Agriculture, Forestry and Fisheries (4).

The Feed Safety Law also requires feed manufacturers to place a Feed Production Manager in each of their plants that manufacture feed containing antimicrobial feed additives. Qualified veterinarians or pharmacists, those who have completed university studies in pharmaceutical, veterinary, animal or agrochemical science and those who have been engaged in feed production for over three years and have passed a training course organised by the FAMIC are qualified to be a Feed Production Manager.

Table I shows the antimicrobial feed additives approved by the Minister of Agriculture, Forestry and Fisheries and their target animals. By the end of May 2009, 25 antimicrobials had been approved as feed additives. Nine of the approved antimicrobial feed additives are also used in human medicine. The other 16 are used only in animals. Monensin sodium and 18 other antimicrobial feed additives are permitted for use in feed for layers, but they are not allowed to be used when layers are in egg production. Colistin sulfate and 19 other additives are permitted for use in feed for broilers but are not allowed to be used during the seven days prior to slaughter for human consumption. Tylosin phosphate and 14 other additives can be used in feed for pigs up to 70 kg and until 7 days prior to slaughter for human consumption. Zinc bacitracin and 3 other additives are permitted for use in feed for cattle less than 3 months of age. Zinc bacitracin and 4 other additives can be used in feed for cattle less than 6 months of age and until 7 days before being slaughtered for human consumption (1).

Antimicrobials for veterinary medicine

Antimicrobials used for therapeutic purposes and for the prevention of parasitic and protozoan diseases are subject to regulation by the Pharmaceutical Affairs Law. In accordance with this law:

- A person who intends to manufacture and market veterinary medicinal products in Japan must obtain prior approval for each particular product that is to be manufactured and marketed from the Minister of Agriculture, Forestry and Fisheries. Approval of each medicinal product is made in consultation with the Pharmaceutical Affairs and Food Sanitation Council. In order for an antimicrobial to be approved as a veterinary medicinal product, it must be safe and effective when administered to target animals affected with target diseases and it is not supposed to have a high risk of emergence of antimicrobial resistance. Antimicrobials are approved on condition that they are used for a maximum of seven days.

- Veterinary medicinal products that are antimicrobials (except those used for aquaculture) are designated as antimicrobials that require a prescription issued by a veterinarian in order to be marketed.
- Antimicrobials must be used in line with the usage, dosage, withdrawal period and other conditions prescribed by the Minister of Agriculture, Forestry and Fisheries.

In addition, the Veterinary License Law prescribes that veterinarians shall not issue prescriptions for antimicrobials without physically examining the animals.

Risk assessment of antimicrobials for prevention of emergence and spread of bacterial resistance

In October 2002, the Agricultural Production Materials Council adopted a policy to cancel the approval of antimicrobial feed additives which have the potential to select for antimicrobial-resistant bacteria that are human pathogens. In response to this decision, the

Table I
Approved antimicrobial feed additives and their target animals

Antimicrobial	Target animals: Layers (weeks of age)	Broilers (weeks of age)		Pigs (kg)		Cattle (months of age)		
	<10	<3	>=3	<30	30-70	<3	3-6	>=6
Sedecamycin*				×	×			
Tylosin phosphate*				×				
Alkyltrimethylammonium calcium oxytetracycline*	×	×		×		×	×	
Chlortetracycline*	×	×				×	×	
Destomycin A*				×	×			
Salinomycin sodium	×	×	×	×	×		×	×
Semduramicin sodium	×	×	×					
Narasin	×	×	×					
Monensin sodium	×	×	×				×	×
Lasalocid sodium	×	×	×					×
Zinc bacitracin*	×	×	×	×	×	×	×	
Colistin sulfate*	×	×	×	×	×	×		
Nosiheptide	×	×	×	×	×			
Virginiamycin*	×	×	×	×	×			
Flavophospholipol	×	×	×	×	×			
Enramycin	×	×	×	×	×			
Avilamycin	×	×	×	×	×			
Efrotomycin				×	×			
Bicozamycin	×	×	×	×	×			
Amprolium plus ethopabate	×	×	×					
Amprolium plus ethopabate and sulfaquinoxaline*	×	×	×					
Morantel citrate				×	×			
Decoquinate	×	×	×					
Nicarbazin		×						
Calcium halofuginone polystyrenesulfonate	×	×	×					

* antimicrobials with an asterisk are those that are also used in human medicine
× the antimicrobial in the left column is permitted for use in feed for the target animals specified at the top at specified amounts

Ministry of Agriculture, Forestry and Fisheries (MAFF) requested the Food Safety Commission in December 2003, to assess the risk of 29 antimicrobial feed additives and 34 antimicrobial veterinary medicinal products that belong to the same family and have demonstrated cross-resistance with the feed additives.

In September 2004, the Food Safety Commission developed a guideline for the assessment of the risk of selection of antimicrobial-resistant bacteria by the use of antimicrobials in livestock production. Based on this guideline, the Food Safety Commission is conducting risk assessments of antimicrobial-resistant bacteria. Depending on the result of the risk assessments, the MAFF takes one of the following measures for risk management (Fig. 2):

- no change from the current measures
- cancellation of the approval as feed additives or veterinary medicinal products
- enhancement of risk management measures (e.g. reduction of the target feed and animals, restriction of use, shortening of the application period).

In September 2006, the Food Safety Commission assessed the risk of emergence of antimicrobial resistance as negligible by the use of a feed additive (monensin sodium). As a result, the MAFF introduced no change from the current measures.

Antimicrobial resistance monitoring

The Japanese Veterinary Antimicrobial Resistance Monitoring (JVARM) programme, an antimicrobial resistance monitoring programme in food-producing animals, has been in force since fiscal year 2000.

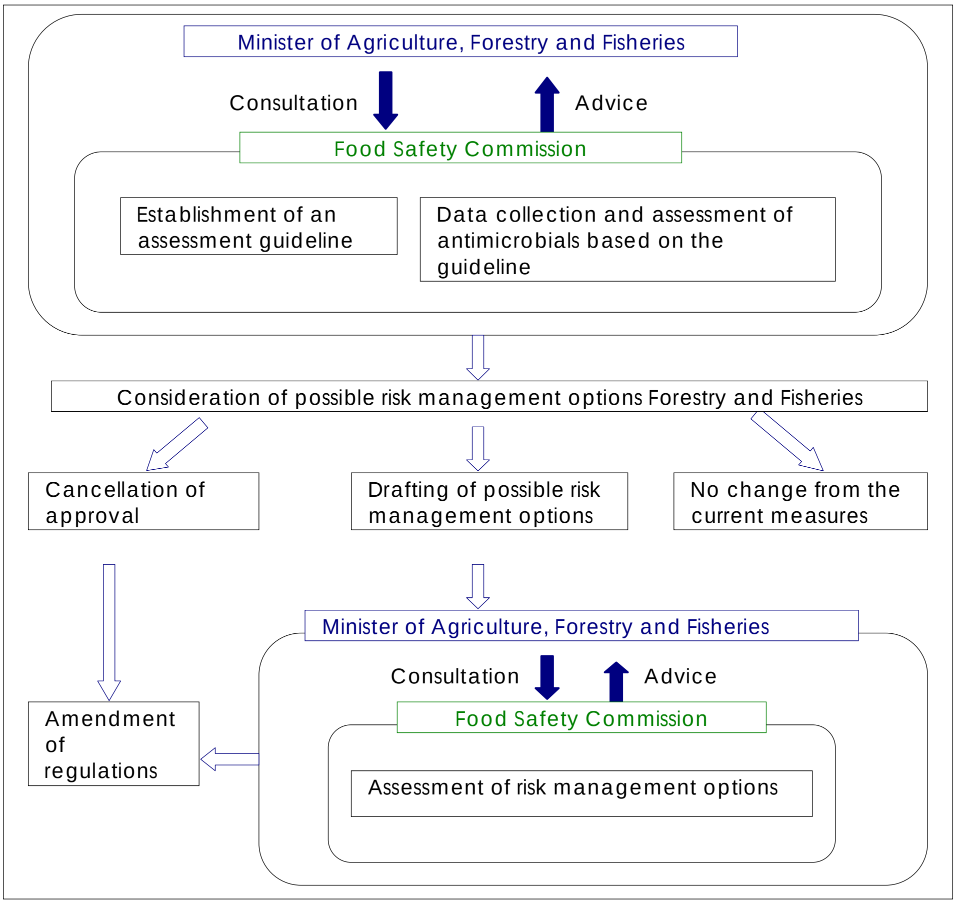

Figure 2
Procedure for risk assessment and management of antimicrobial feed additives and veterinary antimicrobial products for antimicrobial resistance control

The objectives of JVARM are as follows:

- to monitor the emergence and spread of antimicrobial resistance in bacteria in food-producing animals
- to monitor the effectiveness of antimicrobials for target animal diseases
- to monitor the amount of antimicrobials used in food-producing animals
- to collect information required for the risk analysis of resistant bacteria
- to promote the prudent use of antimicrobials in food-producing animals.

The JVARM is composed of the three following activities:

- monitoring of the amounts of antimicrobials used in animals
- monitoring of resistance in zoonotic and indicator bacteria isolated from apparently healthy animals
- monitoring of resistance in animal pathogens isolated from diseased animals.

The National Veterinary Assay Laboratory (NVAL) and FAMIC are engaged in the JVARM in collaboration with prefecture Livestock Hygiene Service Centres (LHSCs). The prefecture LHSCs are responsible for isolation and identification of bacteria and for minimum inhibitory concentration (MIC) measurement. The LHSCs despatch results and resistant bacteria to the NVAL and FAMIC which serve as reference laboratories and are responsible for the preservation of resistant bacteria and compilation of results. The NVAL also provides training courses to train prefecture LHSC officials in the isolation, identification and MIC measurement of bacteria (2).

Monitoring of the amount of antimicrobials used in animals

Under the Pharmaceutical Affairs Law, pharmaceutical companies that produce and/or import veterinary antimicrobial products are required to submit data on the amounts that they manufacture and/or import and market to the MAFF every year. The annual amount of active ingredients of approved antimicrobials used in animals is calculated based on these data. In 2003, a total of 860 metric tons of veterinary antimicrobial products were marketed in Japan. Figure 3 shows the annual amounts of different antimicrobials marketed in Japan from 2000 to 2003. The amount of veterinary antimicrobial products marketed in Japan peaked in 2001 and has been on the decline since then. Figure 4 gives the amount of antimicrobials marketed in Japan by target animals. Pigs are the major target species of antimicrobials, followed by aquatic animals and broiler chickens.

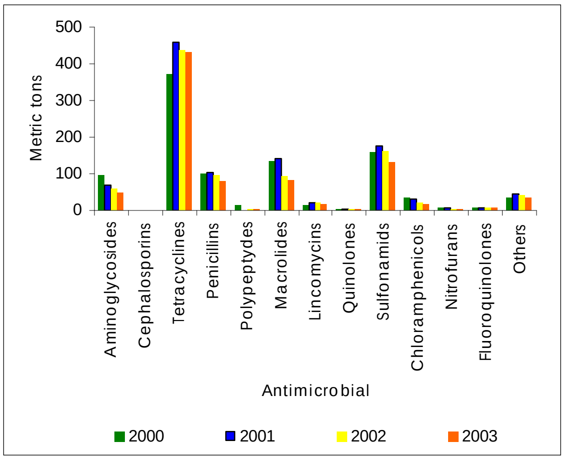

Figure 3
Annual quantities of antimicrobial veterinary medicinal products marketed in Japan by antimicrobial from 2000 to 2003

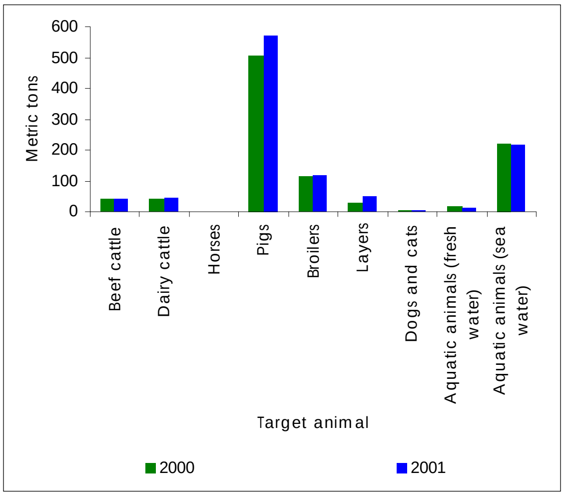

Figure 4
Annual quantities of antimicrobials marketed in Japan by target animals in 2000 and 2001

Monitoring of antimicrobial resistance in bacteria from apparently healthy animals

Salmonella species, *Campylobacter jejuni* and *C. coli* (zoonotic bacteria) and *Escherichia coli*, *Enterococcus faecium* and *E. fecalis* (indictor bacteria) are subject to antimicrobial susceptibility testing. The zoonotic and indicator bacteria are isolated from faecal samples collected from four types of food-producing animals (cattle, pigs, broilers and layers). Each prefecture is allocated one the four bacteria (*Salmonella*, *Campylobacter*, *Escherichia coli* or *Enterococcus*) each year and is required to collect six samples from each animal type for the bacterium allocated in that year, with each sample collected from different farms. Two strains are isolated from one sample for antimicrobial susceptibility testing. Thus, a total of approximately 600 strains (2 strains × 6 samples × 4 animal types × 47/4 prefectures) are isolated for antimicrobial susceptibility testing every year for each bacterium. The MICs of the bacteria tested are determined by the agar dilution method described by the Clinical Laboratory Standards Institutes (CLSI, formerly NCCLS) (5). The MIC data are interpreted using the most current breakpoints from the CLSI guidelines. When no CLSI interpretative criteria are available, epidemiological breakpoints defined from MIC distribution are used.

Table II shows the number of strains isolated from apparently healthy animals for each zoonotic and indicator bacterium. *E. coli* was isolated from almost all faecal samples. A slightly smaller number of *Enterococcus* was isolated than for *E. coli*. *Campylobacter* was isolated from approximately 30% of the faecal samples. *Salmonella* was isolated from 10% to 45% of broiler samples and less than 10% of other animal samples (Fig. 5).

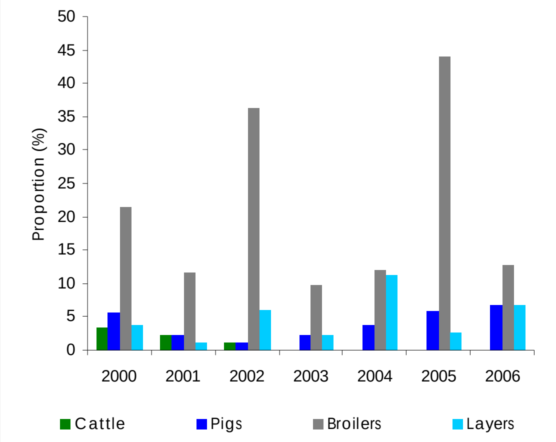

Figure 5
Proportion of faeces from healthy animals from which *Salmonella* was isolated by year between 2000 and 2006

The proportion of resistant *Salmonella* strains for different antimicrobials is shown in Figure 6. Of the 15 antimicrobials used for susceptibility testing, resistance was observed in nine antimicrobials. The highest resistance was observed in dihydrostreptomycin (DSM), followed by oxytetracycline (OTC), kanamycin (KM), trimethoprim (TMP) and bicyclomycin (BCM). There was no *Salmonella* strain that was resistant to fluoroquinolones. A small number of strains were resistant to cephalosporines (CEZ) (3).

Table II
Number of strains isolated from faecal samples from healthy animals subjected to monitoring from fiscal year 2000 to 2006

Fiscal years	*Escherichia coli*	*Enterococcus*	*Campylobacter*	*Salmonella*
2000	620	556	302	91
2001	580	302	239	22
2002	532	246	168	50
2003	475	286	247	20
2004	511	513	219	35
2005	518	562	158	41
2006	500	421	83	64

Source: National Veterinary Assay Laboratory, Ministry of Agriculture, Forestry and Fisheries (1)

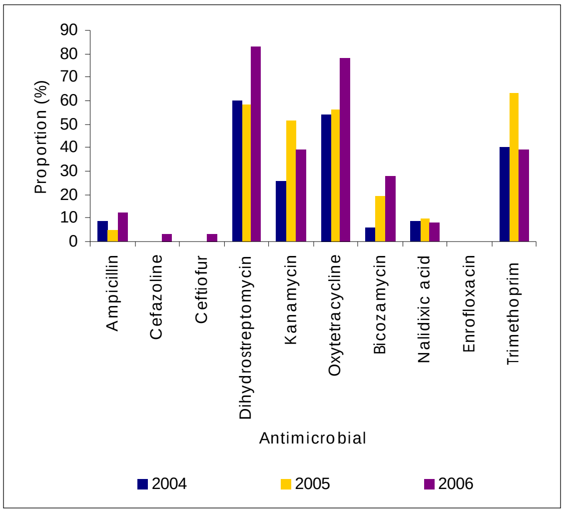

Figure 6
Proportion of resistant *Salmonella* strains of total *Salmonella* strains isolated from healthy animals

The proportion of resistant *Escherichia coli* strains for different antimicrobials is given in Figure 7. Of the 15 antimicrobials used for susceptibility testing, resistance was observed in 13 antimicrobials. The highest resistance was observed in OTC (45%) followed by DSM (30%) (3). The proportion of resistant *Enterococcus* strains for different antimicrobials is shown in Figure 8.

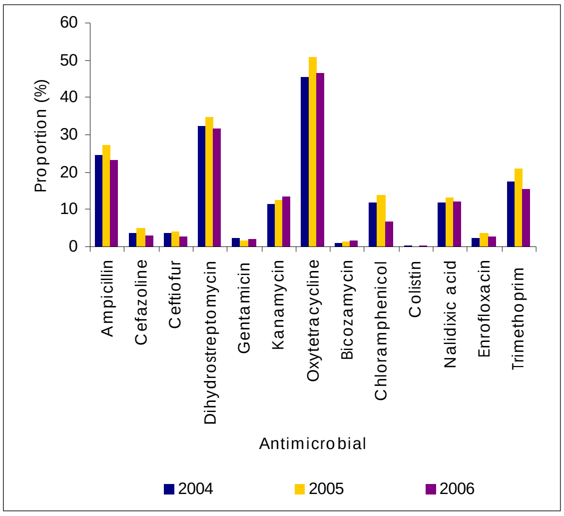

Figure 7
Proportion of resistant *Escherichia coli* strains of total *E. coli* strains isolated from healthy animals

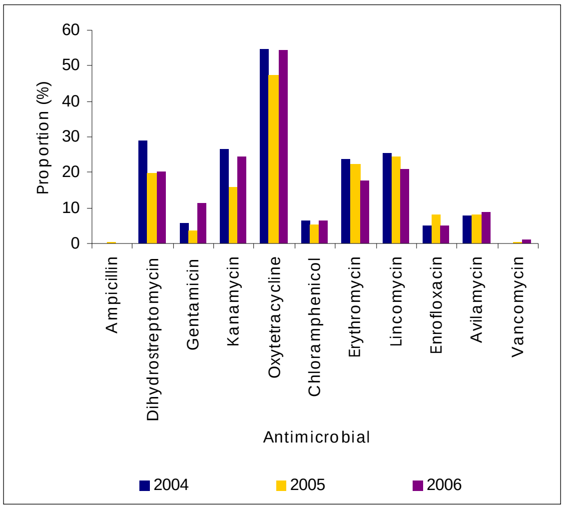

Figure 8
Proportion of resistant *Enterococcus* strains of total *Enterococcus* strains isolated from healthy animals

Figure 9 provides the proportion of faeces from which *Campylobacter* was isolated for different types of animals. *Campylobacter* was isolated more often from pig and chicken faeces than from cattle faeces. *C. jejuni* was mainly isolated from cattle and poultry, whereas *C. coli* was mainly observed in pigs. The proportion of resistant *C. jejuni* and *C. coli* strains for different antimicrobials is given in Figure 10. In general, more *C. coli* strains had antimicrobial resistance than *C. jejuni* strains. Only *C. coli* strains showed resistance to erythromycin (EM) (3).

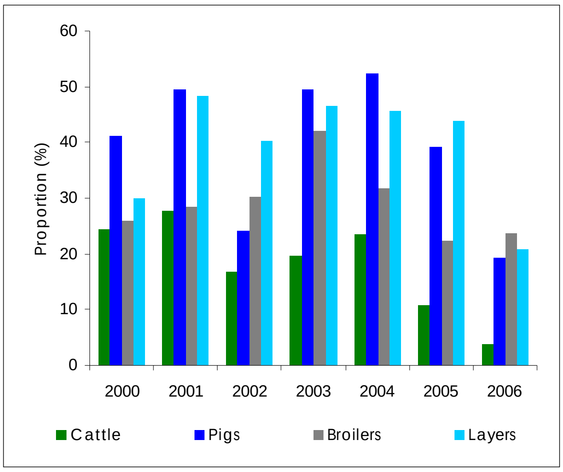

Figure 9
Proportion of faeces samples in which *Campylobacter* was isolated from different animals

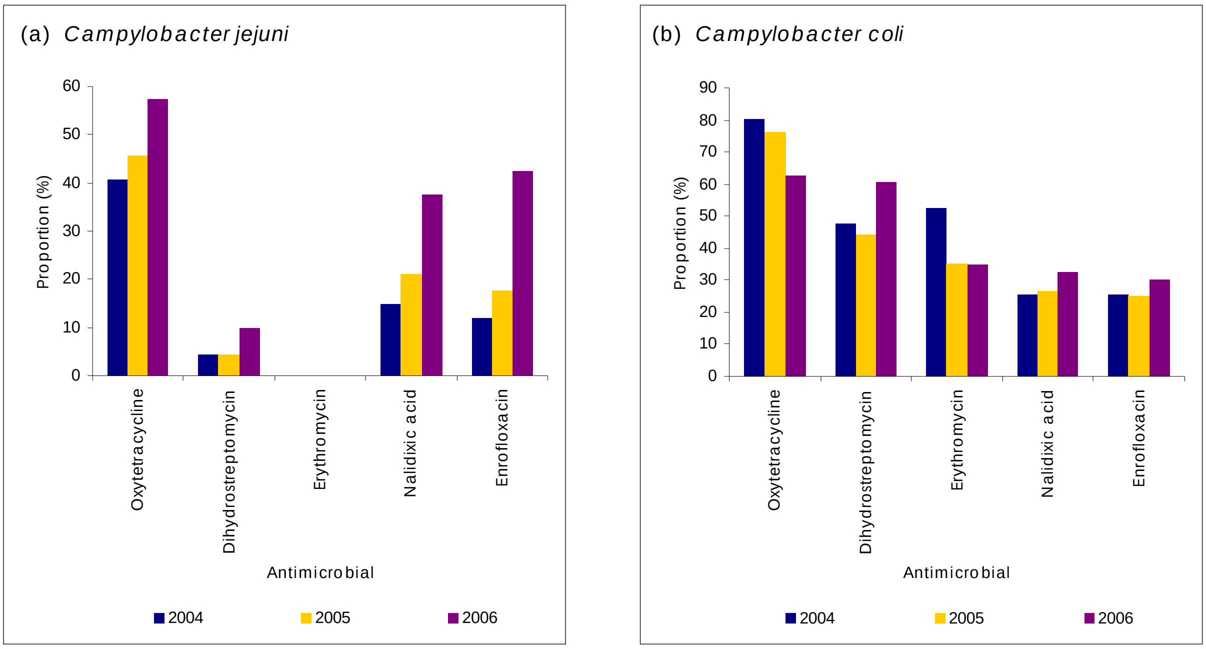

Figure 10
Proportion of resistant *Campylobacter jejuni* and *C. coli* strains of total *C. jejuni* and *C. coli* strains isolated from apparently healthy animals

Monitoring of antimicrobial resistance in animal pathogens

Animal pathogens subjected to monitoring include *Salmonella* species, *Staphylococcus* species, *Actinobacillus pleuropneumoniae*, *Archanobacterium pyogenes*, *Pasteurella multocida*, *Streptococcus* species and *Klebsiella* species (3). Animal pathogens are isolated from samples submitted to prefecture LHSCs for diagnosis and are subjected to antimicrobial susceptibility testing using the procedures described above.

The number of strains subjected to monitoring from fiscal year 2000 to 2006 is given in Table III.

Table III
Number of strains isolated from faecal samples from diseased animals subjected to monitoring from fiscal year 2000 to 2006

Fiscal years	*Actinobacillus pleuro pneumoniae*	*Staphylo-coccus* species	*Strepto-coccus* species	*Escherichia coli*	*Pasteurella multocida*	*Pseudomonas*	*Salmonella*
2000	85	88	61	–*	–*	–*	–*
2001	25	–*	–*	53	14	–*	60
2002	28	–*	–*	84	13	8	79
2003	25	38	23	51	11	5	72
2004	33	24	21	72	27	–*	73
2005	–*	45	–*	43	–*	–*	128
2006	–*	32	–*	54	–*	–*	111

Source: National Veterinary Assay Laboratory, Ministry of Agriculture, Forestry and Fisheries (1)
* the bacterium was not subjected to monitoring in that year

The proportion of resistant *Salmonella* strains for different antimicrobials of the total strains tested is shown in Figure 11. *Salmonella* strains isolated from diseased animals were more resistant to ampicillin (ABPC) than strains isolated from healthy animals. This was because resistant strains were mostly *S.* Typhimurium, *S.* Choleraesuis and *S.* Dublin isolated from cattle and pigs and were resistant to ABPC (3).

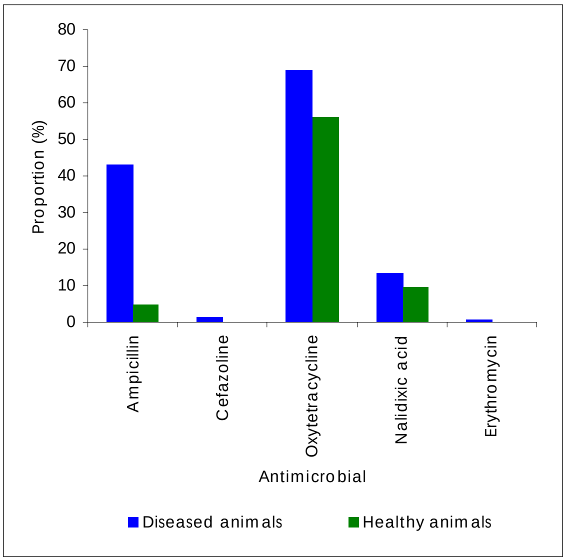

Figure 11
Proportion of resistant *Salmonella* strains for different antimicrobials of total *Salmonella* strains isolated from diseased animals

The proportion of resistant *Staphylococci* strains for different antimicrobials of the total strains tested is shown in Figure 12. Approximately 30% and 20% of *Staphylococci* strains isolated from diseased animals were resistant to penicillin (PC) and OTC, respectively. Less than 10% of *Staphylococci* strains isolated from diseased animals were resistant to other antimicrobials (3).

Conclusion

An Expert Workshop on non-human antimicrobial usage and antimicrobial resistance held jointly by the World Health Organization (WHO), Food and Agriculture Organization (FAO) and World Organisation for Animal Health (*Office International des Épizooties*: OIE) in December 2003 concluded that there is clear evidence of the human health consequences due to resistant organisms resulting from non-human usage of antimicrobials (6). This conclusion has affected many countries in their positions in addressing the risk management of antimicrobial resistance. The results obtained from JVARM in recent years have been used to monitor the evolution of antimicrobial susceptibility of animal pathogens and other bacteria in food-producing animals. These results provided grounds for the prudent use of antimicrobials in veterinary medicine and thus contributed to the maintenance of the effectiveness of antimicrobials in veterinary medicine. In the future, the results obtained from JVARM will provide scientific data for the assessment of the risk of emergence and spread of resistant bacteria in human medicines and the selection of risk management options to control antimicrobial resistance through the use of antimicrobials in food-producing animals.

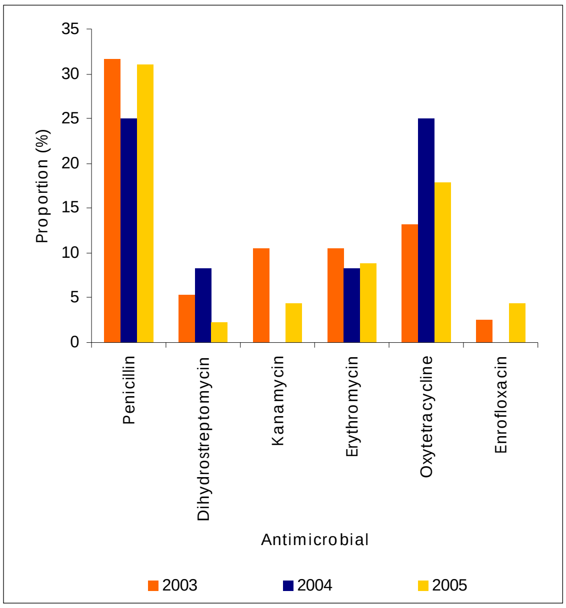

Figure 12
Proportion of resistant *Staphylococcus* strains for different antimicrobials of total *Staphylococcus* strains isolated from diseased animals

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