Sales of veterinary antimicrobial agents for therapeutic use in food-producing animal species in Japan between 2005 and 2010

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Summary

The use of veterinary antimicrobial agents in animals can result in the emergence and selection of resistant bacteria in food-producing animals. This study elucidated the use of veterinary antimicrobial agents in Japan in terms of milligrams of active ingredient sold per kilogram of biomass between 2005 and 2010. Data on sales of antimicrobial agents and on the biomass of the target animal species were compiled from statistics published by the Japanese Ministry of Agriculture, Forestry and Fisheries. The quantities of antimicrobials used varied between animal species: the highest usage was observed in pigs (392 to 423 mg/kg), followed by beef cattle (45 to 67 mg/kg), broiler chickens (44 to 63 mg/kg) and dairy cattle (33 to 49 mg/kg). For the animal species combined, usage of third- and fourth-generation cefalosporins, fluoroquinolones and macrolides ranged from 0.10 to 0.14 mg/kg biomass, 1.1 to 1.3 mg/kg biomass and 7.8 to 10.6 mg/kg biomass, respectively.

Keywords

Animal biomass – Antimicrobial resistance – Japan – Surveillance – Veterinary antimicrobial.

Introduction

In Japan, as in most countries, antimicrobials are used in human and veterinary medicines, and in agriculture and aquaculture. Any use of antimicrobials, be it in humans, animals, plants or in food processing, can lead to bacterial resistance. Increased antimicrobial resistance in bacteria that cause infections in humans is a threat to public health. Concern has been expressed with regard to the use of antimicrobials in animal production (1, 2), as this may lead to the selection of resistant bacteria. Such bacteria may then spread to humans through the consumption of food of animal origin and ultimately reduce or nullify the therapeutic effect of antimicrobials in human medicine (3, 4).

Analysis of data generated from surveillance of the use of veterinary antimicrobials is essential for the identification and quantification of risk factors for the emergence and selection of resistant bacteria in food-producing animals (5). Data on the use of antimicrobials can be combined with data on the prevalence of resistance and used to develop policies for the control of antimicrobial resistance (6).

The use of antimicrobials as measured in kilograms cannot be directly compared between countries and animal species because of differences in the potencies and pharmacokinetics of antimicrobials, and differences in livestock demographics. Several methods have been proposed for evaluating the exposure of animals to antimicrobials. One such method is the use of the animal daily dose (ADD), which corresponds to the defined daily dose in the human health sector, and is the defined average maintenance dose of a specific antimicrobial per kilogram of a specified animal per day, applied for its main indication (7). By expressing the use of veterinary antimicrobials as the number of ADDs, comparison of the total antimicrobial use in different countries becomes possible. An alternative method is to calculate the quantity of active ingredients used per kilogram of animal biomass. A further option is the use of the population correction unit, which is a proxy for the animal biomass potentially treated with antimicrobial agents (8). Although these methods do not enable correction of the quantity of antimicrobials in terms of potency or pharmacokinetics, they provide a simple means of comparison of the use of veterinary antimicrobials between countries and species, corrected for livestock demographics.

The total usage of veterinary antibacterial agents in Japan in terms of milligrams of active ingredient sold per kilogram of animal biomass has been analysed previously (9). In the present study, data on sales of antibacterials between 2005 and 2010, categorised by animal species at national level, were analysed to compare the amounts used in different species. Because third- and fourth-generation cefalosporins, fluoroquinolones and macrolides are considered by the World Health Organization (WHO) to be critically important in human medicine (10), sales of these antibacterials were analysed in detail by animal species.

Methods

In Japan, manufacturers and importers of veterinary antimicrobials are required, under the Regulations for Control of Veterinary Pharmaceutical Products (Ministerial Order No. 3, 1961), to report annually to the Minister of Agriculture, Forestry and Fisheries on the quantity of veterinary antimicrobials sold for therapeutic use. Data submitted must include the names of the antimicrobial products, routes of administration, concentrations of the active ingredient in each product and the target animal species in which the products are used (11). In the present study, sales data between 2005 and 2010 were compiled as quantities of active ingredient by antimicrobial class and animal species (dairy cattle, beef cattle, pigs, broiler chickens). Based on the anatomical therapeutic chemical classification system for veterinary medicinal products (ATCvet), proposed by WHO (12), the antimicrobial agents were classified into 13 groups: tetracyclines, amphenicols, penicillins, sulfonamides, macrolides, lincosamides, aminoglycosides, pleuromutilins, cefalosporins, trimethoprim, polymyxins, quinolones, and others. The specific classification used in this study is shown in Table I.

The total biomass of beef cattle, pigs and broiler chickens and the numbers of dairy cattle were compiled from statistics published by the Ministry of Agriculture, Forestry and Fisheries (13, 14). The biomass of beef cattle and pigs was considered as the carcass weight, being the whole body weight of a slaughtered animal after bleeding, evisceration and skinning. For broiler chickens, the only data available were for total live slaughter weights; therefore, the biomass was calculated by multiplying the live slaughter weight by a conversion factor of 0.70, representing the proportion of carcass weight after bleeding, plucking and evisceration, compared with the live slaughter weight (15). Data on the total carcass weight or slaughter weight of dairy cattle are not available; therefore, the biomass was calculated by multiplying the numbers of dairy cattle in Japan by the average weight (635 kg) of Holstein and Jersey dairy cattle (16); these two breeds represent more than 99% of all dairy cattle in Japan (16). A decision was made to use carcass weight for broiler chickens and live weight for dairy cattle to make the results directly comparable with those in a European study in 2010 (17), where carcass weight was used for beef cattle, pigs and broiler chickens, and live weight for dairy cattle. The method used for calculating the biomass of dairy cattle in the present study was the same as that in the European study (17).

Usage of veterinary antibacterial agents was expressed as weight in milligrams of active ingredient sold per total biomass of dairy and beef cattle, pigs and broiler chickens per year. The quantities of antimicrobial agents used in individual animal species were based on sales data of antimicrobial classes and the biomass of the target species.

Results

Between 2005 and 2010, the total quantity of veterinary antimicrobials sold for therapeutic use in dairy and beef cattle, pigs and broiler chickens in Japan varied between 600 and 687 tonnes (Table II). The proportions of antimicrobials sold were as follows: tetracyclines 46% to 51%, sulfonamides 14% to 18%, penicillins 8% to 11%, aminoglycosides and macrolides 5% to 7%, lincosamides 4% to 6%, amphenicols and trimethoprim 2% to 3%, pleuromutilins 1% to 3%, polymyxins 0.3% to 1.6%, quinolones 0.7% to 0.9%, cefalosporins 0.3% to 0.5%, others 0.01% to 0.06%. The quantities sold for therapeutic use in each target animal species are shown in Figure 1. The largest amount was sold for pigs (490 to 527 tonnes), followed by broiler chickens (55 to 75 tonnes), dairy cattle (32 to 52 tonnes) and beef cattle (23 to 33 tonnes).

The biomass (estimated live weight) of dairy cattle was between 942,000 and 1,051,000 tonnes and declined between 2005 and 2010 (Fig. 2). The biomass of broiler chickens was between 1,191,000 and 1,285,000 tonnes and increased during the same period. Biomasses of beef cattle and pigs were approximately 500,000 and 1,300,000 tonnes respectively and remained stable during that period (Fig. 2).

The quantities of veterinary antimicrobials sold for therapeutic use in the animal species studied, expressed in relation to the biomass of the respective animal species, are shown in Figure 3. The highest usage was seen in pigs (392 to 423 mg/kg), followed by beef cattle (45 to 67 mg/kg), broiler chickens (44 to 63 mg/kg) and dairy cattle (33 to 49 mg/kg).

Figures 4, 5 and 6 show the sales quantities of third- and fourth-generation cefalosporins, fluoroquinolones and macrolides, respectively, per biomass of the target species. The overall mean sales of cefalosporins per biomass of the combined animal species increased slightly from 0.10 to 0.14 mg/kg biomass during the period 2005 to 2010. The highest sales were for use in pigs (Fig. 4): quantities per biomass increased by 37.5% from 0.24 mg/kg in 2009 to 0.33 mg/kg in 2010. In contrast, usage in beef cattle decreased by 42.9% from 0.21 to 0.12 mg/kg in the same period. Mean quantities of fluoroquinolones per biomass of the animal species combined were stable between 2005 and 2010, ranging from 1.1 to 1.3 mg/kg biomass, though between 2008 and 2010 sales per biomass were greater for broiler chickens than for pigs (Fig. 5). Mean sales of macrolides per biomass of the combined species increased slightly from 7.8 mg/kg biomass in 2006 to 11 mg/kg biomass in 2010 and were highest for pigs (Fig. 6).

Discussion

In a previous related study, the total usage of antimicrobial agents in food-producing animals in Japan was found to be relatively high compared with that of most European countries (9). The present study shows that usage of antimicrobials in pigs was about ten times higher than in other food-producing animals (Fig. 3), and this accounts for the relatively high overall usage of antimicrobials in food-producing animals in Japan. As the proportion of pig biomass is smaller in Japan than in most European countries (17), the analysis suggests that the use of antimicrobials in pigs in Japan is higher than in European countries; however, the quantities of antimicrobials sold for each target animal species in Europe are not available (17). In addition, variations in prescribing patterns and in the frequency and significance of bacterial pig diseases might explain the observed differences between Japan and European countries.

The quantity of tetracyclines (236 to 273 tonnes) sold for use in pigs was the highest of the veterinary antimicrobials sold in Japan: 235 to 271 tonnes were sold as peroral administration and 1.0 to 1.4 tonnes as injections. Tetracyclines are readily available at low prices and are widely used for the treatment of respiratory diseases caused by *Actinobacillus pleuropneumonia* and *Pasteurella multocida* (18, 19); however, tetracyclines are not generally used for enteric diseases caused by *Escherichia coli* or *Salmonella* spp., as these bacteria are often resistant to tetracyclines (20, 21). In Denmark, where the biomass of pig meat is 1.5 times greater than in Japan, the purpose of antimicrobial treatment in pigs is mainly for enteric disease (22). Thus, the frequency and significance of bacterial respiratory diseases in Japan might contribute to the frequent use of tetracyclines.

Sales of third- and fourth-generation veterinary cefalosporins, veterinary fluoroquinolones and macrolides in Japan were comparable with those in European countries, although the denominators used to estimate the amount per animal were not identical: in the present study biomass was used as the denominator, whereas in a study in nine European countries the population correction unit was used (8). In 2009, sales of third- and fourth-generation cefalosporins were higher in Japan than in Sweden and Denmark, but lower than in other European countries (the Netherlands, France, Switzerland, the Czech Republic, the United Kingdom [UK]) (8). In the same year, fluoroquinolone sales in Japan were lower than in the Czech Republic but higher than in other European countries (France, Switzerland, the Netherlands, the UK, Denmark, Norway, Finland, Sweden) (8), and macrolide sales were lower than those in the Netherlands and France but higher than in other European countries (the Czech Republic, the UK, Denmark, Switzerland, Finland, Sweden) (8).

In the present study, the use of veterinary antimicrobial agents was expressed as milligrams of active ingredient per kilogram of biomass and did not take into account any differences in potency and pharmacokinetics of the various agents. Thus, these results should not be used as the sole basis for setting management priorities but should always be complemented by data from other sources. It should also be noted that the unit used was a technical unit of measurement and not a real value for populations of animals that could potentially be treated with antimicrobials. For measurement of the true exposure of food animals to antimicrobials, the use of ADDs is preferable because this takes into account any differences in potency and pharmacokinetics, and consequently the dosage prescription of different antimicrobials.

Despite these caveats, and in the absence of an internationally accepted standard approach for reporting antimicrobial usage, the method used in the present study provides a simple method for comparison between years, countries and animal species of the quantities of antimicrobials sold for therapeutic purposes per kilogram of biomass (7, 9, 23).

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Table I
The classifications of antimicrobials in this study

Antimicrobial class	Antimicrobials
Tetracyclines	Chlortetracycline; doxycycline; oxytetracycline
Amphenicols	Chloramphenicol; florfenicol; thiamphenicol
Penicillins	Amoxicillin; ampicillin; aspoxicillin; benzylpenicillin; cloxacillin; dicloxacillin; mecillinam; nafcillin; tobicillin
Sulfonamides	Homosulfamine; sulfachlorpyridazine; sulfadiazine; sulfadimethoxine; sulfadimidine; sulfadoxine; sulfamerazine; sulfamethoxazole; sulfamethoxypyridazin; sulfamonomethoxin; sulfamoyldapsone; sulfaquinoxalin; sulfisozole
Macrolides	Acetylisovaleryl tylosintartrate; erythromycin; josamycin; mirosamycin; spiramycin; terdecamycin; tilmicosin; tylosin
Lincosamides	Clindarmycin; lincomycin
Aminoglycosides	Apramycin; dihydrostreptomycin; fragiomycin; gentamicin; kanamycin; spectinomycin; streptomycin
Pleuromutilins	Tiamulin; valnemulin
Cefalosporins	Cefapirin; cefaronium: cefazolin; cefovecin; cefquinome; ceftiofur; cefuroxime; cefalexin; cefapirin
Trimethoprim	Ormethoprim; trimethoprim
Polymyxins	Colistin
Quinolones	Danofloxacin; difloxacin; enrofloxacin; lomefloxacin; marbofloxacin; nalidixic acid; norfloxacin; ofloxacin; orbifloxacin; oxolinic acid
Others	Bacitracin; bicozamycin; fosfomycin; miloxacin; nanafrocin; nifurstyrenic acid: nitrofurazone: novobiocin; thiostrepton

Table II
Weights of veterinary antimicrobial agents, in tonnes of active substance, sold for therapeutic use in Japan, 2005 to 2010

Antimicrobial class	2005	2006	2007	2008	2009	2010
Tetracyclines	340.2	321.2	326.8	278.7	306.2	287.9
Amphenicols	15.1	16.2	15.7	16.5	18.1	19.7
Penicillins	66.1	56.9	48.3	46.1	64.3	67.0
Sulfonamides	122.3	113.1	106.7	105.2	117.9	88.5
Macrolides	36.0	31.3	32.2	37.0	36.0	42.7
Lincosamides	28.5	36.2	38.1	34.9	37.1	38.6
Aminoglycosides	46.0	38.7	34.1	39.2	42.2	34.0
Pleuromutilins	7.3	10.9	13.5	16.0	16.8	19.1
Cefalosporins	2.0	2.8	2.6	2.6	2.8	3.1
Trimethoprim	14.3	16.1	15.4	15.4	15.9	12.8
Polymyxins	3.5	4.7	2.1	2.7	8.8	10.1
Quinolones	5.3	5.3	5.5	5.3	4.6	4.9
Others	0.4	0.4	0.3	0.4	0.3	0.05
Total	687.0	653.8	641.4	599.9	670.9	628.5

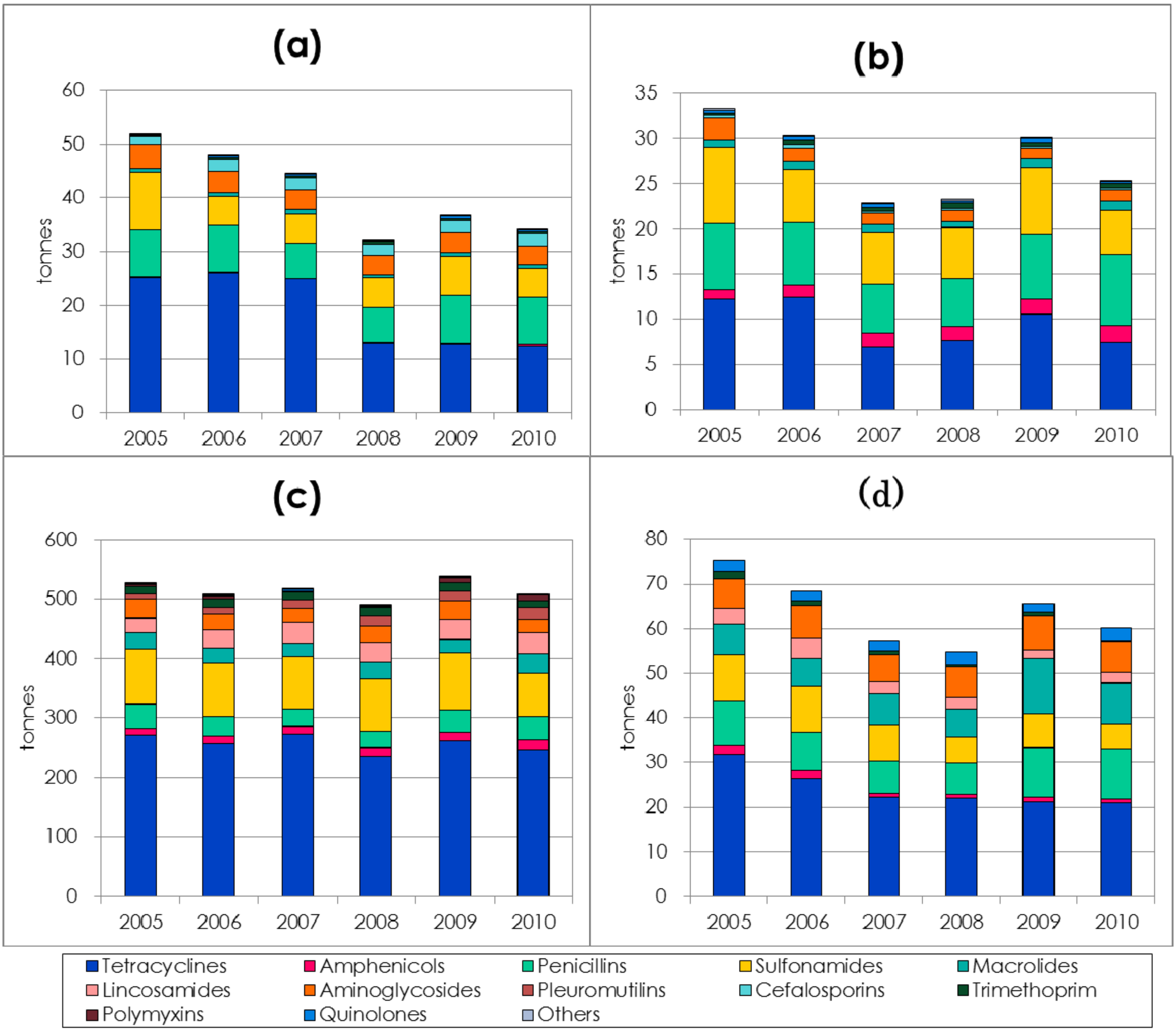


Fig. 1

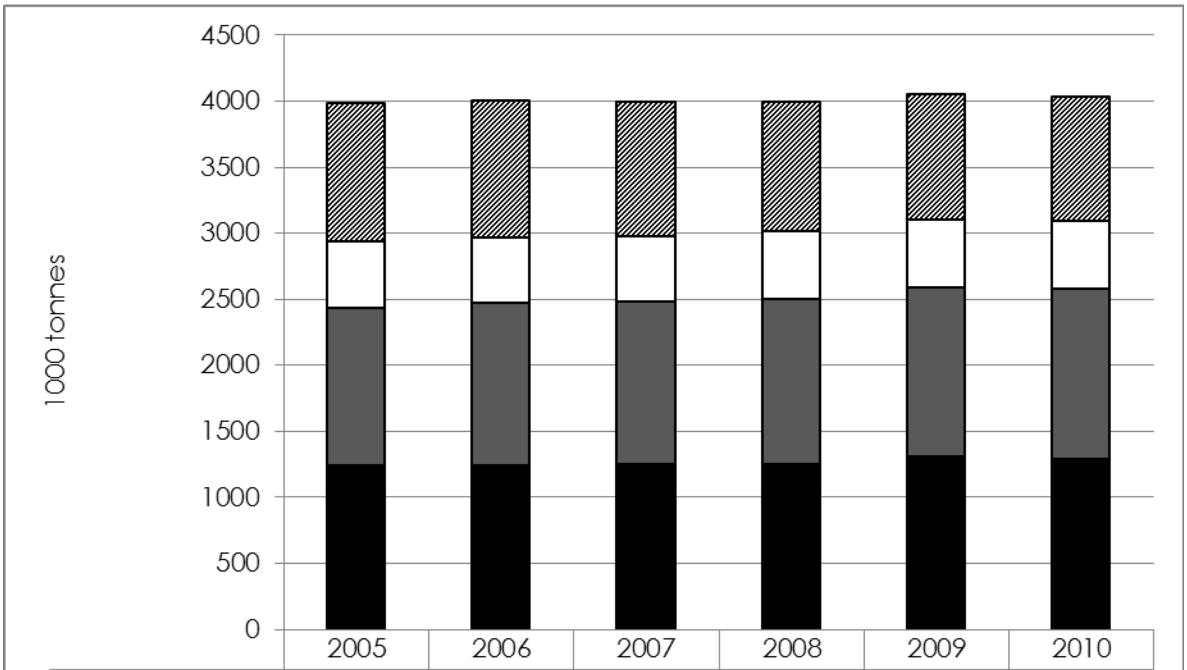
Weights of veterinary antimicrobial agents, in tonnes of active substance, sold for therapeutic use in Japan, 2005 to 2010

a) Dairy cattle

b) Beef cattle

c) Pigs

d) Broiler chickens



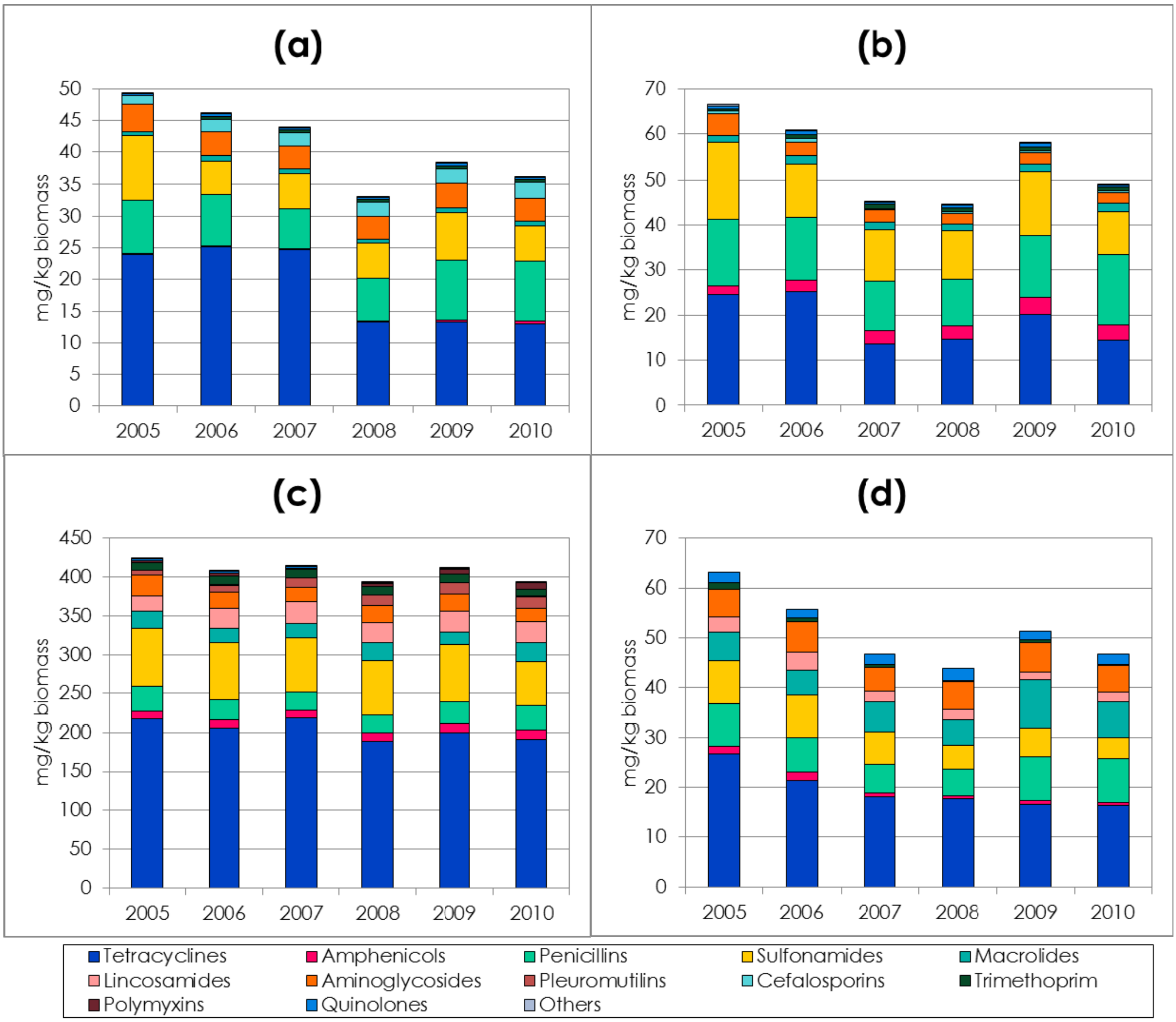
	2005	2006	2007	2008	2009	2010
Dairy cattle	1051	1039	1011	973	953	942
Beef cattle	499	497	504	520	517	515
Broiler chickens	1191	1225	1228	1251	1279	1285
Pigs	1245	1247	1251	1249	1310	1292

Fig. 2

Estimated live weight of dairy cattle and biomass of beef cattle, broiler chickens and pigs produced in Japan, 2005 to 2010

Fig. 3
Quantities of veterinary antimicrobial agents sold for therapeutic use in Japan in mg/kg biomass of the respective target species, 2005 to 2010

a) Dairy cattle
b) Beef cattle
c) Pigs
d) Broiler chickens



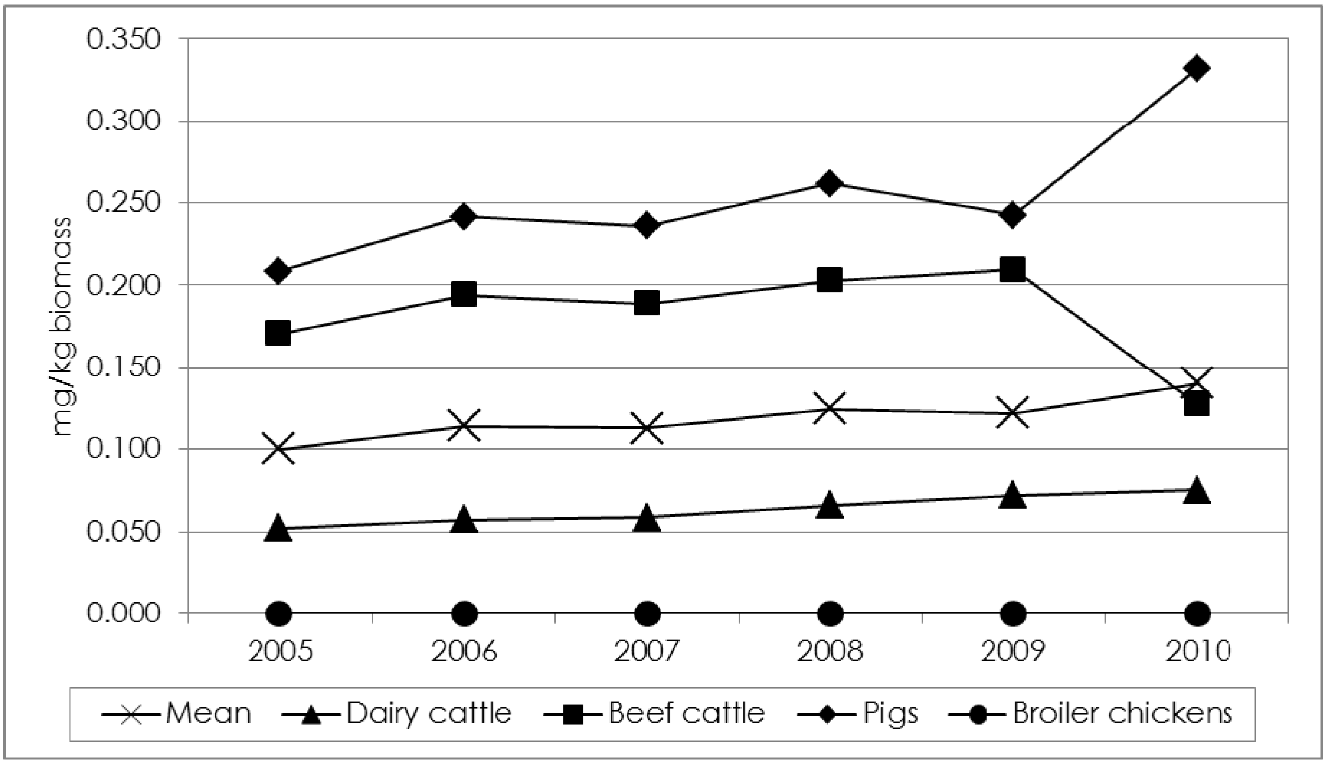


Fig. 4
Quantities of third- and fourth-generation veterinary cefalosporins sold in Japan in mg/kg biomass of target species, 2005 to 2010

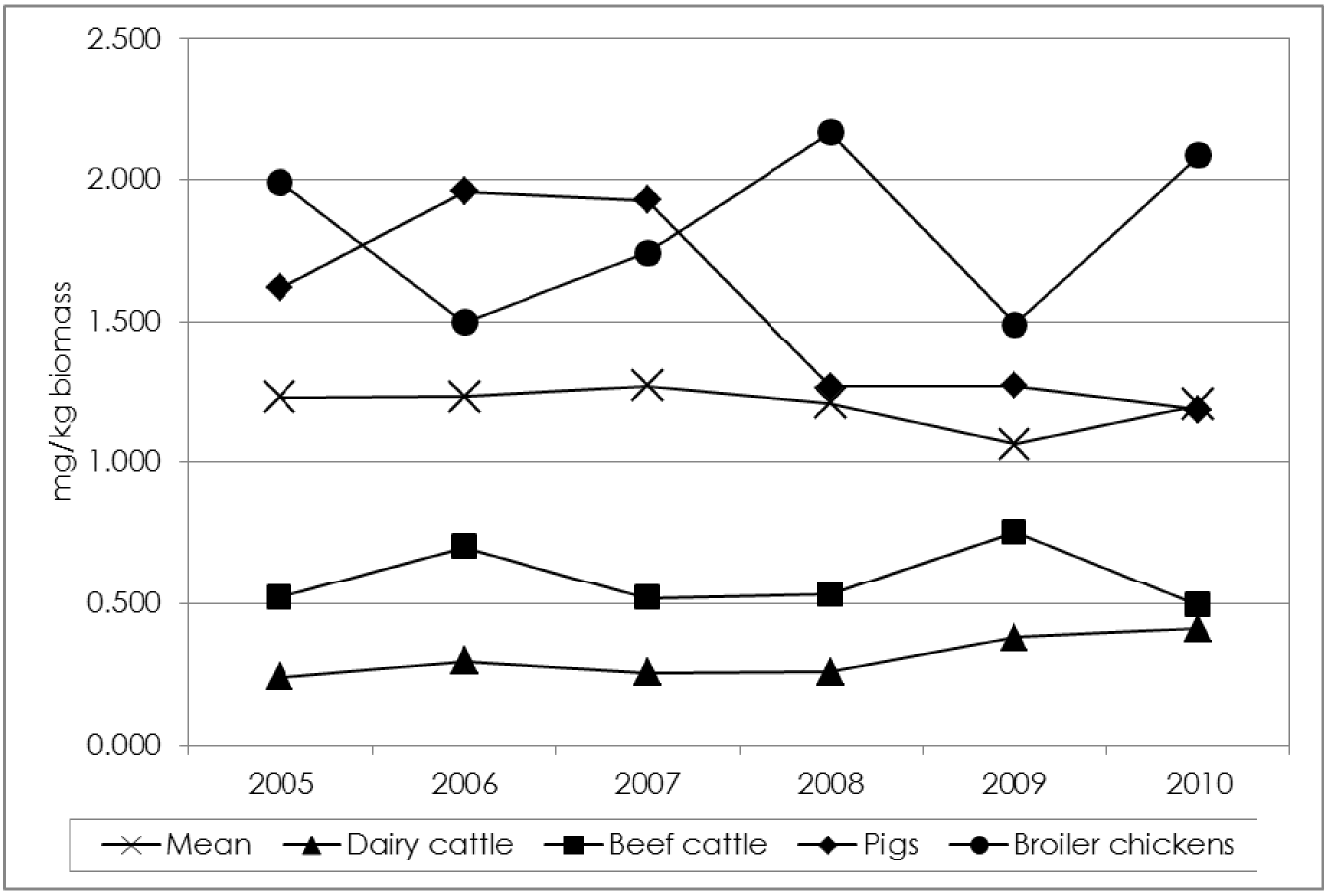


Fig. 5

Quantities of veterinary fluoroquinolones sold in Japan in mg/kg biomass of target species, 2005 to 2010

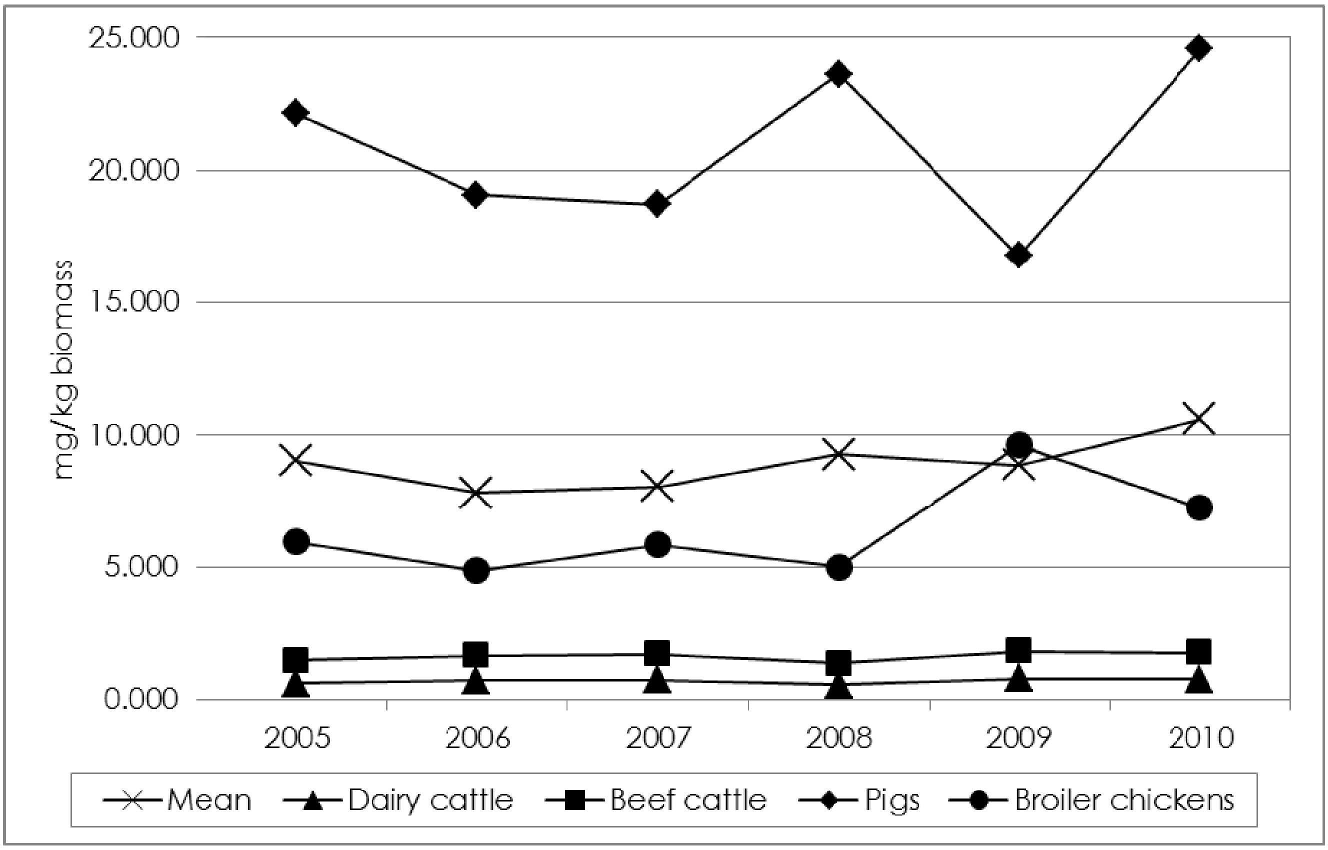


Fig. 6

Quantities of veterinary macrolides sold in Japan in mg/kg biomass of target species, 2005 to 2010