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Epidemiology

Evaluation of antimicrobial use in dairy cattle, beef cattle and broilers in Japan using dosage-based indicators

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ABSTRACT. The sales amount of antimicrobials intended for use in dairy cattle, beef cattle and broilers from 2008 to 2019 was evaluated for each antimicrobial class and administration route using dosage-based indicators. Our results revealed that the antimicrobial sales amount sold for use in dairy cattle in 2019 in terms of total weight of active ingredient, the number of defined daily doses (DDDs) (theoretical amount of biomass subjected to antimicrobial treatment in a year) and the number of treatment days (TDs) (theoretical number of days of treatment that an animal is subjected to in a year) calculated using Japanese DDD values (DDDjp values) was 36,751 kg, 8,261,848,000 kg·days and 15.5 days, respectively. Likewise, the antimicrobial sales amount sold for use in beef cattle and broilers in 2019 in terms of these metrics was 33,403 kg, 3,928,248,000 kg·days and 3.61 days, and 69,773 kg, 2,947,848,000 kg·days and 10.66 days, respectively. There was a considerable difference between the number of DDDs calculated using DDDjp values and that calculated using European DDD values (DDDvet values) for antimicrobial products sold for use in dairy and beef cattle. Our results also revealed that the sales amount of some antimicrobials, such as cephalosporins and quinolones represented larger proportions when calculated using dosage-based indicators than when calculated using the weight of active ingredient. Considering that Japanese veterinarians and farmers are more likely to conform to the Japanese dosage recommendations rather than the European ones, these results indicate the need for using dosage-based metrics, in particular metrics based on Japanese dosages rather than European dosages.

KEY WORDS: antimicrobial use, broiler, cattle, defined daily dose, Japan

Emergence of antimicrobial resistance in bacteria is a global public and animal health challenge. If no proactive solutions are taken, some 10 million people could die of drug resistant infections each year by 2050 [18]. Antimicrobial use is considered a major driver of selection and emergence of resistant bacteria [7]. Therefore, reducing the use of antimicrobials in humans and animals is important to lower the selection pressure and thus presence of resistant bacteria. To make sure that antimicrobial use is reduced, monitoring of antimicrobial use is essential in both humans and animals.

Currently much work is undertaken to reach a global consensus on antimicrobial use data collection and reporting methods in food-producing animals. The EU member countries report quantities of antimicrobials sold in food-producing animals as mg of active ingredient, adjusted by kg of animal biomass called population correction unit (PCU) [5]. The PCU is calculated by multiplying the numbers of livestock animals and slaughtered animals by the theoretical weight at the most likely time of treatment [5].

Using the national sales data, the antimicrobial use in food-producing animals (dairy cattle, beef cattle, pigs and broilers) from 2005 to 2017 in Japan was quantified in terms of mg of active ingredient per kg of biomass and found to be relatively high compared with the usage in most European countries [11, 19]. This metric is relatively easy to calculate when one has data on antimicrobial sales amount and demographic data of animals, and enables to make comparison of antimicrobial use between countries and years. However, this metric does not reflect the potency of antimicrobial agents, favoring the use of potent antimicrobials in order to lower usage amount while selection pressure does not change.

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In recent years, dosage-based indicators, metrics that take account of antimicrobial potency, have been developed and used in some countries to monitor antimicrobial use in food-producing animals. In human medicine, defined daily dose (DDD) value refers to the assumed average maintenance dose per day for a drug used for its main indication in adults and is assigned for each medicine by WHO [24]. As for antimicrobials intended for use in food-producing animals, the European Medicines Agency (EMA) assigned DDD value (DDDvet value) for each active ingredient, each food producing species (cattle, swine and poultry) and administration route based on the dosage data of nine European countries [3]. Some European countries including Denmark and the Netherlands use dosage-based indicators to monitor antimicrobial use at national level and farm level [17, 19]. We have previously assigned DDD values (DDDjp values) for antimicrobial agents for use in pigs in Japan by active ingredient and administration route, and using these DDDjp values and national sales data, quantified the number of DDDjps administered in pigs [1]. We have recently assigned DDDjp values for antimicrobial agents for use in cattle and poultry in Japan by active ingredient, administration route and number of active ingredients in the product [6].

In this study, using these DDDjp values and national sales data, we quantified the number of DDDjps for dairy and beef cattle and broilers for each year from 2008 to 2019. Using the number of DDDjps, we calculated the average treatment days per year (TDjps) for these species during these years. We also calculated the same metrics using DDDvet values to test the effects of using either DDDjp or DDDvet values for different administration routes and antimicrobial classes.

MATERIALS AND METHODS

Collection of the antimicrobial use data

The sales amounts of antimicrobials for dairy cattle, beef cattle and broilers from 2008 to 2019 were calculated in the same way as we did for pigs in our previous study [1], by retrieving sales data provided by the National Veterinary Assay Laboratory and compiling these data into the sales amount of active ingredient by antimicrobial class, administration route and animal species in which the products were used [15]. In compiling the sales data, the antimicrobial agents were classified into 13 groups based on the Anatomical Therapeutic Chemical classification system for veterinary medicinal products (ATCvet) proposed by WHO [23]: tetracyclines; amphenicols; penicillins; sulfonamides; macrolides; lincosamides; aminoglycosides; pleuromutilins; cephalosporins; trimethoprim; polymyxins; quinolones; and others.

Assignment of DDDjp values

To calculate the number of DDDs, we used the DDDjp values that we recently assigned for antimicrobial agents for use in pigs, cattle and poultry by active ingredient, administration route and number of active ingredients in the product (single substance and combination products) [6]. Since sales amounts of an active ingredient for single substance and combination product are not reported separately in the sales data, we assigned the DDD value of an active ingredient which is used both in single substance and combination products by averaging the DDDjp values for single substance and combination products based on the number of products marketed in Japan, in the same way as we did in assigning the DDD values for antimicrobial agents for pigs [1]. The list of the DDDjp values used in this study is provided in Supplementary Table 1.

Calculation of the number of DDDjps

We calculated the number of DDDs using DDDjp values (number of DDDjps) for each active ingredient and administration route from 2008 to 2019, in the same way as we did for pigs in our previous study [1], by dividing the weight of active ingredient by the corresponding DDDjp value. The number of DDDs presents the theoretical amount of biomass (kg·days) subjected to antimicrobial treatment in a year, assuming that the antimicrobial products are used in the target species according to the dosage specified in the summary of product characteristics.

Calculation of TDjps

The average number of treatment days (TDs) presents the theoretical number of days of treatment that an animal of target species is subjected to in a year. The TDjps were calculated by dividing the number of DDDjps by the average number of animals of target species and the average weight of animals at treatment:

$$\text{TDjps} = \frac{\text{Number of DDDjps(kg·days)}}{\text{Number of animals of target species}\left(\text{animals}\right) \times \text{Average weight of animals of target speceis at treatment (kg / animal)}}$$

where the number of animals and average weight at treatment of target species (dairy cattle, beef cattle and broilers) are presented in Table 1.

Calculation of the number of DDDvets and TDvets

The number of DDDs and TDs were also calculated using DDDvet values. The list of DDDvet values are available on the EMA website [4]. To calculate the number of DDDvets for those antimicrobial ingredients for which DDDvet is not available (see Supplementary Table 1), DDDjp value was used instead. Then the DDDvet value of an active ingredient which is used both in single substance and combination products was assigned by averaging the DDDvet values for single substance and combination products based on the number of products used in assigning the DDDjp values. The number of DDDvets and TDvets were not calculated for antimicrobials for intramammary and intrauterine routes because DDDvet values for these antimicrobials are defined

Table 1. Average weight at treatment and number of dairy cattle, beef cattle and broilers used in this study

Target species	Number of animals (in 1,000 s)*												Average weight of treatment (kg)
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	
Dairy cattle	998	985	964	933	943	923	893	870	871	852	847	839	635**
Beef cattle	2,890	2,923	2,892	2,763	2,723	2,642	2,567	2,489	2,479	2,499	2,514	2,503	435***
Broilers	102,987	107,141	107,141	107,141	107,141	131,624	135,747	135,747	134,395	134,923	138,776	138,228	2.0****

*The data on the number of raised animals was available from Livestock Statistics [12]. Since the data on the number of broilers for 2010 to 2012 and in 2015 were not available, the number of broilers for 2009 and 2014 were used respectively for these years. **Average weight at treatment of dairy cattle was estimated based on the average weight of dairy cows in 2014 [10], assuming that dairy cows are subjected to treatment when they are grown up. ***Average weight at treatment of beef cattle was estimated as follows: The average weights of treatment for Japanese black, Japanese brown and other beef breed cattle were estimated to be 405 kg, 493 kg and 412 kg, respectively based on the Beef Cattle Rearing Standards [13]. The average weights of treatment for Holstein breed beef cattle were estimated to be 467 kg based on the Beef Cattle Rearing Standards [13]. The average weight of treatment for cross breed beef cattle was estimated to be 515 kg based on the data published by Association for the Future of the Livestock Sector in Japan [2]. The average weight at treatment of beef cattle was estimated to be 435 kg as the weighted average of these average weights according to the number of respective species as of February 2021 based on Livestock Statistics (Japanese Black: 1,735,000; Japanese Brown: 23,330; Japanese Shorthorn: 33,500; Holstein: 267,900; and crossbreed: 495,400) [12]. ****Average weight at treatment of broilers was estimated as the average of the average weights of treatment for male broilers (2.14 kg) and female broilers (1.77 kg) from one-week old to seven-week-old based on the Poultry Rearing Standards [14], assuming that broilers have an equal chance of being subjected to treatment at any age until two weeks before shipment.

Table 2. Antimicrobial sales amount in dairy cattle in 2019 quantified using different metrics by antimicrobial class and administration route

Antimicrobial class	Total			Parenteral					Oral					Intramammary/Intrauterine		
	Weight of active ingredient (kg)	Number of DDDjp (1,000 s)	TDjps	Weight of active ingredient (kg)	Number of DDDjp (1,000 s)	Number of DDDvet (1,000 s)	TDjps	TDvets	Weight of active ingredient (kg)	Number of DDDjp (1,000 s)	Number of DDDvet (1,000 s)	TDjps	TDvets	Weight of active ingredient (kg)	Number of DDDjp (1,000 s)	TDjps
Tetracyclines	14,566	1,635,715	3.07	387	64,539	59,574	0.12	0.11	14,070	1,469,199	735,238	2.76	1.38	108	101,976	0.19
Amphenicols	1,010	98,086	0.18	973	90,690	71,295	0.17	0.13	37	7,396	822	0.01	0	0	0	0
Penicillins	8,085	1,786,399	3.35	5,433	910,888	584,088	1.71	1.1	2,340	345,480	109,183	0.65	0.2	312	530,032	0.99
Sufonamides	4,859	134,207	0.25	597	20,566	22,832	0.04	0.04	4,262	113,641	113,641	0.21	0.21	0	0	0
Macrolides	1,377	99,228	0.19	486	65,256	102,434	0.12	0.19	891	33,972	24,746	0.06	0.05	0	0	0
Lincosamides	6	78,740	0.15	0	0	0	0	0	0	0	0	0	0	6	78,740	0.15
Aminoglycosides	2,868	1,009,885	1.9	2,171	255,058	155,531	0.48	0.29	102	11,534	7,238	0.02	0.01	594	743,292	1.39
Pleuromutilins	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cephalosporins	2,942	3,170,306	5.95	1,770	419,074	500,416	0.79	0.94	0	0	0	0	0	1,172	2,751,231	5.16
Trimethoprim	525	139,576	0.26	5	827	827	0	0	520	138,749	138,749	0.26	0.26	0	0	0
Polymyxins	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Quinolones	453	106,873	0.2	424	103,106	102,521	0.19	0.19	29	3,767	3,118	0.01	0.01	0	0	0
Others	61	2,835	0.01	24	1,584	1,584	0	0	38	1,251	1,251	0	0	0	0	0
Total	36,751	8,261,848	15.5	12,271	1,931,588	1,601,101	3.62	3	22,289	2,124,989	1,133,986	3.99	2.13	2,192	4,205,271	7.89

TDjps: Number of treatment days calculated using Japanese defined daily dose (DDDjp) values. TDvets: Number of treatment days calculated using European defined daily dose (DDDvet) values. The absence of DDDvet values for intramammary and intrauterine products in mg/kg did not allow calculation of the number of DDDvets and the number of treatment days using DDDvet values (TDvets) for this administration route, and consequently, the total number of DDDvets and TDvets.

on one unit per udder or animal basis and are not available in mg per kg per day [4].

Excel version 16.46 (Microsoft Corp.) was used to calculate the weight of active ingredient, the number of DDDs and TDs and to create associated graphs.

RESULTS

Antimicrobial sales amount for use in dairy cattle quantified using different metrics in 2019

The calculated results of the weight of active ingredient, numbers of DDDjps and DDDvets, TDjps and TDvets of the antimicrobial agents sold for use in dairy cattle in 2019 by antimicrobial class and administration route are shown in Table 2. The total weight of active ingredient sold for use in dairy cattle was 36,751 kg; the number of DDDjps was 8,261,848,000 kg·days; and the TDjps was 15.50 days.

Parenteral use: In terms of the weight of active ingredient, parenteral use represented 33.4% of the total use, of which penicillins represented 44.3%, followed by aminoglycosides (17.7%) and cephalosporins (14.4%). In terms of the number of DDDjps and TDjps, parenteral use represented 23.4% of the total use, of which penicillins accounted for 47.2%, followed by cephalosporins (21.7%) and aminoglycosides (13.2%). Of the number of DDDvets and TDvets administered by injection, penicillins accounted for 36.5%, followed by cephalosporins (31.3%) and aminoglycosides (9.71%) (Fig. 1).

Oral use: In terms of the weight of active ingredient, oral use represented 60.6% of the total use, of which tetracyclines represent 63.1%, followed by sulfonamides (19.1%) and penicillins (10.5%). In terms of the number of DDDjps and TDjp, oral use represented 25.7% of the total use, of which tetracyclines represented 69.1%, followed by penicillins (16.3%) and trimethoprim (6.53%). Of the number of DDDvets and TDvets administered orally, tetracyclines represented 64.8%, followed by trimethoprim (12.2%) and sulfonamides (10.0%) (Fig. 1).

Intramammary and intrauterine use: In terms of the weight of active ingredient, intramammary and intrauterine use represented 5.96% of the total use, of which cephalosporins represented 53.5%, followed by aminoglycosides (27.1%) and penicillins (14.2%). In terms of the number of DDDjps and TDjps, intramammary and intrauterin use represented 50.9% of the total use, of which cephalosporins represented 65.4%, followed by aminoglycosides (17.7%) and penicillins (12.6%) (Fig. 1).

Temporal change of antimicrobial sales in dairy cattle from 2008 to 2019 quantified using different metrics

Figure 2 provides the evolution of antimicrobial sales intended for use in dairy cattle from 2008 to 2019 by administration route using different metrics. Regardless of the metrics (the weight of active ingredient, the number of DDDjps, DDDvets, TDjps and TDvets) used, temporal changes between years saw the same trend except for some years, e.g. between 2013 and 2014, the antimicrobial sales for parenteral use decreased in terms of the weight of active ingredient, number of DDDjps and TDjps, but increased in terms of the number of DDDvets and TDvets.

Antimicrobial sales amount for use in beef cattle quantified using different metrics in 2019

The calculated results of the weight of active ingredient, number of DDDs and TDs of the antimicrobial agents sold for use in beef cattle in 2019 by antimicrobial class and administration route are provided in Table 3. The total weight of active ingredient sold for use in beef cattle was 33,403 kg; the number of DDDs calculated using DDDjp was 3,928,248,000 kg·days; the TDs calculated using DDDjp was 3.61 days.

Parenteral use: In terms of the weight of active ingredient, parenteral use represented 37.2% of the total use, of which penicillins represented 37.3%, followed by amphenicols (25.1%) and aminoglycosides (13.2%). In terms of the number of DDDjps and TDjps, parenteral use represented 50.4% of the total use, of which penicillins represented 39.3%, followed by quinolones (18.2%) and amphenicols (15.6%) (Fig. 3). The total number of DDDs and TDs did not differ much regardless of DDDjp or DDDvet values were used. However, there was some variations observed for some antimicrobial classes: larger number of DDDs and TDs were observed for sulfonamides, macrolides and cephalosporins when calculated using DDDvet values than when calculated using DDDjp values (Table 3).

Oral use: In terms of the weight of active ingredient, oral use represented 62.7% of the total use, of which tetracyclines represented 57.2%, followed by sulfonamides (18.6%) and penicillins (12.4%). In terms of the number of DDDjps and TDjps, oral use represented 49.6% of the total use, of which tetracyclines represented 62.0% followed by penicillins (19.8%) and trimethoprim (7.1%) (Fig. 3). The total number of DDDs and TDs were 1.35-fold larger when calculated using DDDjp values than when calculated using DDDvet values (Table 3).

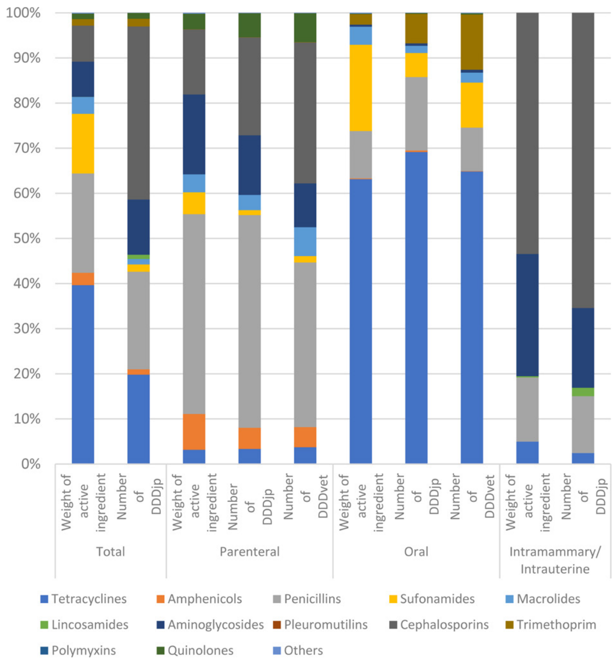

Fig. 1. Relative distribution of antimicrobial sales in dairy cattle in Japan in 2019 showing different antimicrobial classes according to administration route and metric. DDDjp: Japanese defined daily dose; DDDvet: defined daily dose assigned by European Medicines Agency.

Temporal change of antimicrobial sales in beef cattle from 2008 to 2019 quantified using different metrics

Figure 4 provides the evolution of antimicrobial sales intended for use in beef cattle from 2008 to 2019. Regardless of the metrics used, temporal changes between years saw the same trend except for some years, e.g. the antimicrobial sales for parenteral use from 2008 to 2014 saw a remarkable decrease in terms of the weight of active ingredient, but saw a slight decrease when calculated using dosage-based metrics.

Antimicrobial sales amount for use in broilers quantified using different metrics in 2019

The calculated results of the weight of active ingredient, number of DDDs and average treatment days of the antimicrobial agents sold for use in broilers by antimicrobial class and administration route are provided in Table 4. The total weight of active ingredient sold for use in broilers was 69,773 kg; the number of DDDjps was 2,947,848,000 kg·days; the number of DDDvets was 3,105,940,000 kg·days; the TDjps and TDvets were 10.66 and 11.23 days respectively. Assuming that 6 batches of broilers are shipped for slaughter per year [8], the TDs per batch was 1.8 days. Antimicrobials sold for oral use represented 98.8% in terms of weight of active ingredient and 99.2% in terms of the number of DDDjps and TDjps. Figure 5 provides the relative distribution of antimicrobial use between different

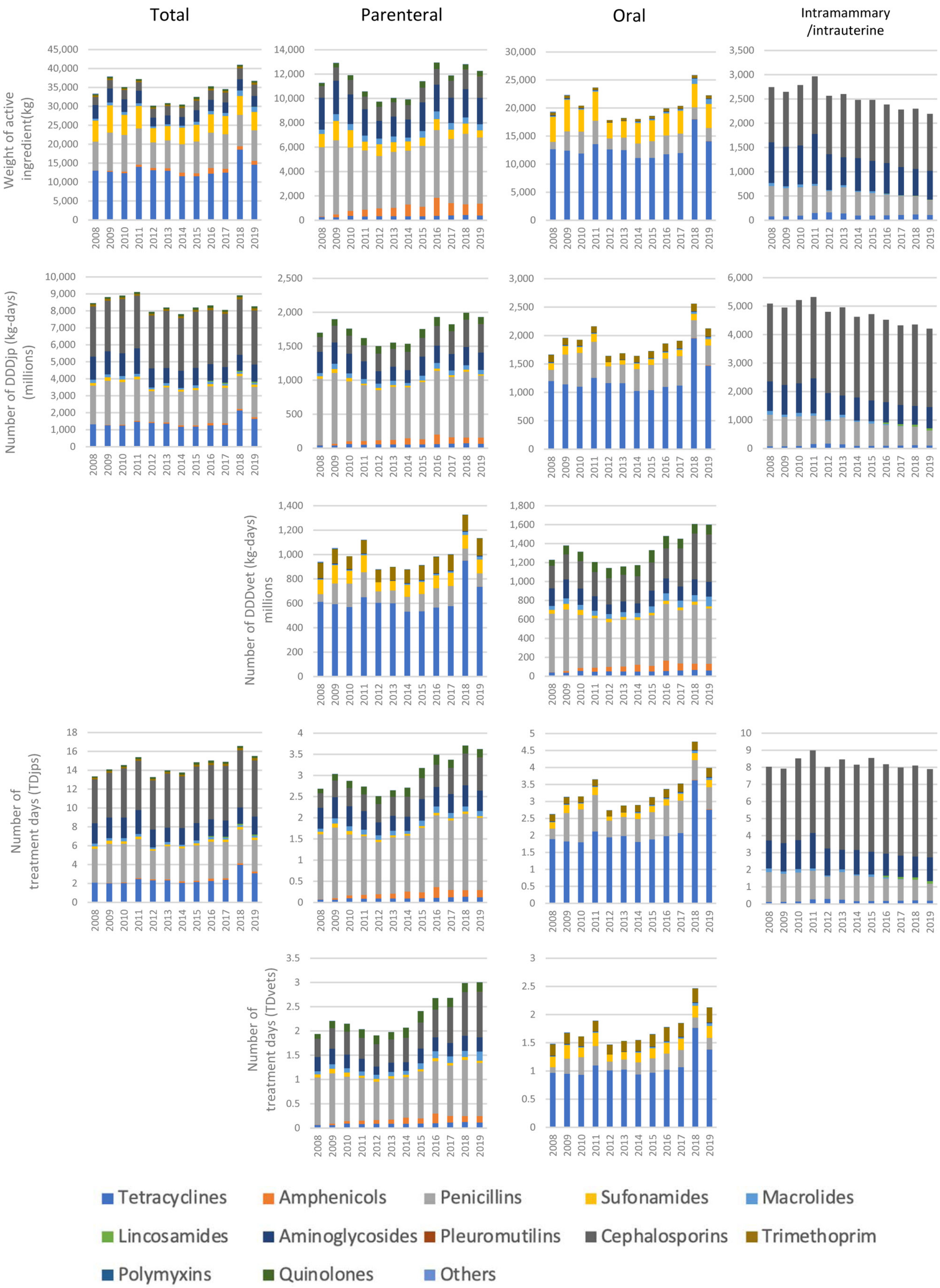

Fig. 2. Evolution of antimicrobial sales for use in dairy cattle in Japan from 2008 to 2019 quantified using different metrics for different administration routes. The absence of DDDvet values for intramammary and intrauterine products in mg/kg did not allow calculation of the numbers of DDDvets and treatment days (TDvets), and consequently the total numbers of DDDvets and TDvets. DDDjp: Japanese defined daily dose; DDDvet: defined daily dose assigned by European Medicines Agency.

Table 3. Antimicrobial sales amount in beef cattle in 2019 quantified using different metrics by antimicrobial class and administration route

Antimicrobial class	Total					Parenteral					Oral				
	Weight of active ingredient (kg)	Number of DDDjps (1,000 s)	Number of DDDvets (1,000 s)	TDjps	TDvets	Weight of active ingredient (kg)	Number of DDDjps (1,000 s)	Number of DDDvets (1,000 s)	TDjps	TDvets	Weight of active ingredient (kg)	Number of DDDjps (1,000 s)	Number of DDDvets (1,000 s)	TDjps	TDvets
Tetracyclines	12,335	1,266,621	1,066,375	1.16	0.98	335	55,775	51,485	0.05	0.05	12,000	1,210,846	1,014,890	1.11	0.93
Amphenicols	3,257	335,736	241,502	0.31	0.22	3,124	309,111	238,544	0.28	0.22	133	26,626	2,958	0.02	0
Penicillins	7,252	1,164,437	621,901	1.07	0.57	4,644	777,768	499,331	0.71	0.46	2,608	386,669	122,570	0.36	0.11
Sufonamides	4,198	114,253	115,328	0.1	0.11	286	9,931	11,005	0.01	0.01	3,912	104,323	104,323	0.1	0.1
Macrolides	2,501	215,527	677,386	0.2	0.62	885	152,954	631,924	0.14	0.58	1,616	62,573	45,462	0.06	0.04
Lincosamides	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Aminoglycosides	1,730	194,460	125,783	0.18	0.12	1,644	184,766	120,385	0.17	0.11	86	9,694	5,398	0.01	0
Pleuromutilins	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cephalosporins	423	124,957	153,642	0.11	0.14	423	124,957	153,642	0.11	0.14	0	0	0	0	0
Trimethoprim	523	139,170	139,170	0.13	0.13	3	422	422	0	0	520	138,749	138,749	0.13	0.13
Polymyxins	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Quinolones	1,071	367,503	273,056	0.34	0.25	1,035	360,331	267,264	0.33	0.25	36	7,172	5,792	0.01	0.01
Others	112	5,584	5,584	0.01	0.01	55	3,696	3,696	0	0	56	1,888	1,888	0	0
Total	33,403	3,928,248	3,419,727	3.61	3.14	12,435	1,979,710	1,977,697	1.82	1.82	20,968	1,948,539	1,442,030	1.79	1.32

TDjps: Number of treatment days calculated using Japanese defined daily dose (DDDjp) values. TDvets: Number of treatment days calculated using European defined daily dose (DDDvet) values.

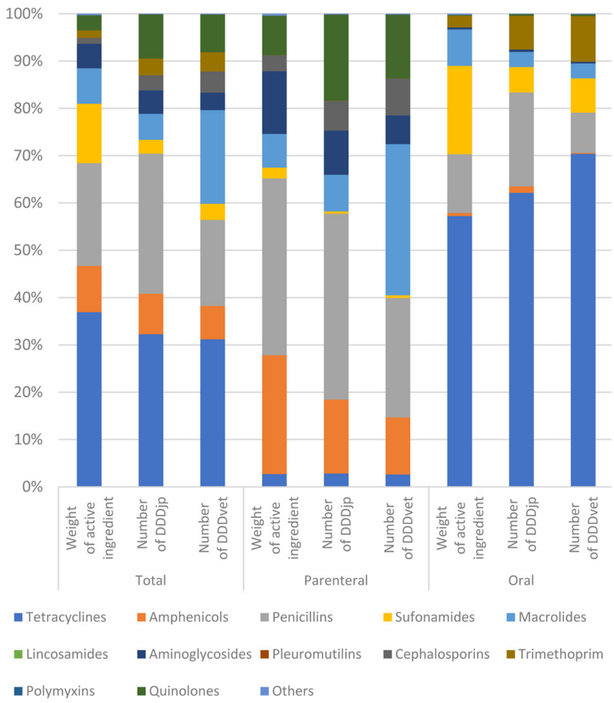

Fig. 3. Relative distribution of antimicrobial sales in beef cattle in Japan in 2019 showing different antimicrobial classes according to administration route and metric. DDDjp: Japanese defined daily dose; DDDvet: defined daily dose assigned by European Medicines Agency.

antimicrobial classes by administration route measured either as the weight of active ingredient or as the number of DDDs.

Parenteral use: The antimicrobial agents sold for parenteral use in broilers were tetracyclines, sulfonamides, trimethoprim and aminoglycosides. In terms of the weight of active ingredient, aminoglycosides represented 79.2%, followed by tetracyclines (19.8%). In terms of the numbers of DDDjps and TDjps, aminoglycosides represented 73.7%, followed by tetracyclines (22.8%) (Fig. 5).

Oral use: Among antimicrobial agents sold for oral use in broilers, tetracyclines represented 39.6% in terms of weigh of active ingredient, followed by penicillins (17.4%) and macrolides (15.0%). In terms of the number of DDDjps and TDjps, tetracyclines represented 28.4%, followed by penicillins (26.5%) and aminoglycosides (10.3%). In terms of the number of DDDvets and TDvets, tetracyclines, penicillin and aminoglycosides accounted for 29.3%, 23.7% and 9.81%, respectively (Fig. 5).

Temporal change of antimicrobial sales in broilers from 2008 to 2019 quantified using different metrics

The evolution of antimicrobial sales from 2008 to 2019 in terms of the weight of active ingredient, the number of DDDs and TDs are presented in Fig. 6. The temporal changes between years saw the same trend regardless of the metrics used, except for some years, e.g. between 2009 and 2010, the antimicrobial sales in terms of the weight of active ingredient and the number of DDDvets decreased, but slightly increased in terms of the number of DDDjps.

Comparison of antimicrobial sales between pigs, dairy cattle, beef cattle, and broilers

Figure 7 shows the evolution of antimicrobial sales for pigs, dairy cattle, beef cattle and broilers from 2008 to 2019 in terms of the weight of active ingredient and number of DDDjps. Data for pigs was retrieved from our previous study [1]. In our previous study [1], we did not calculate the TDs in pigs, because antimicrobials use can be considerably different between sows, weaners and fattening pigs and we thought that calculating the TDs without separating between these production stages would be misleading.

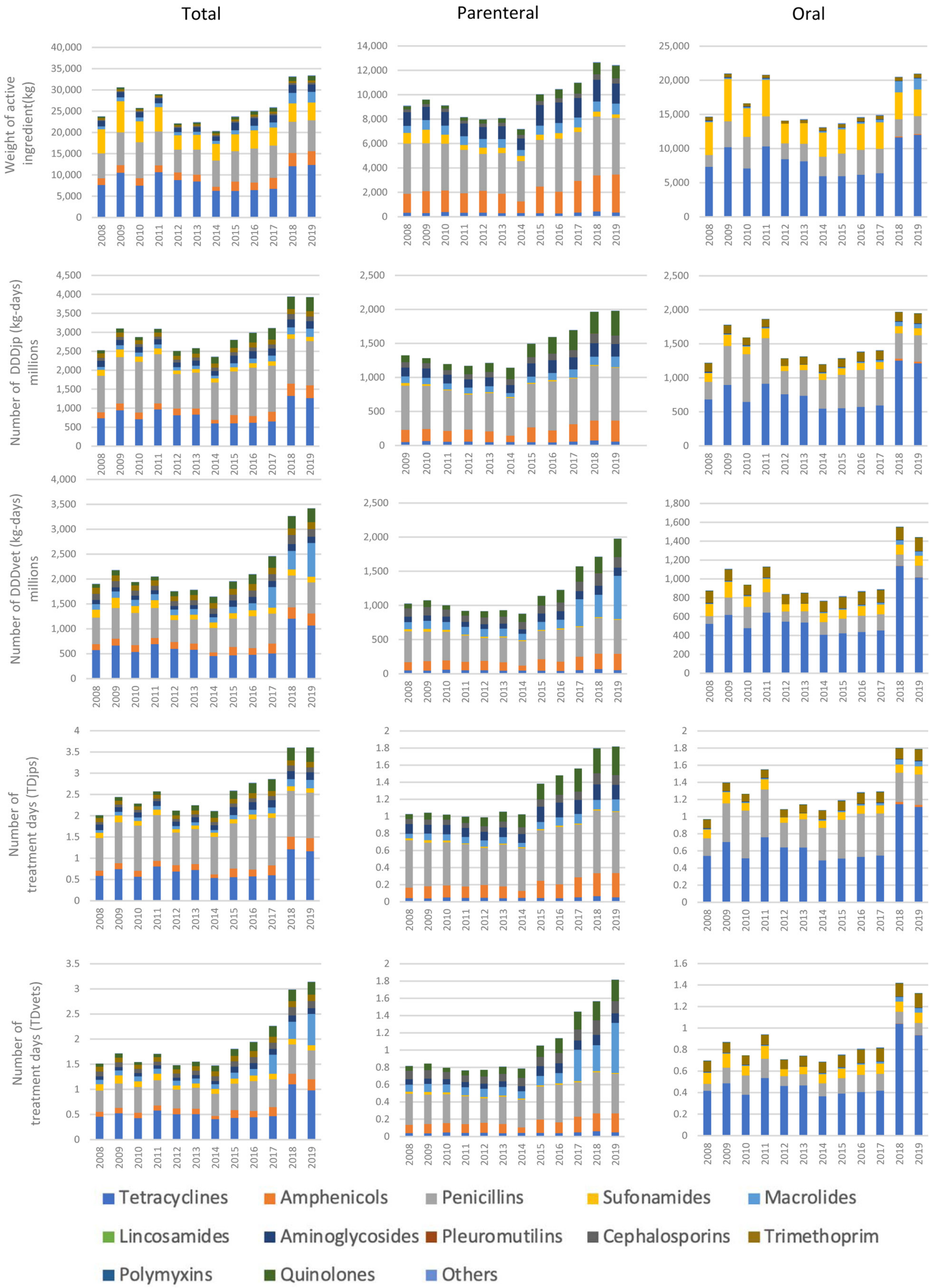

Fig. 4. Evolution of antimicrobial sales for use in beef cattle in Japan from 2008 to 2019 quantified using different metrics for different administration routes. DDDjp: Japanese defined daily dose; DDDvet: defined daily dose assigned by European Medicines Agency.

Table 4. Antimicrobial sales amount in broilers in 2019 quantified using different metrics by antimicrobial class and administration route

Anrtimicrobial class	Total					Parenteral*			Oral				
	Weight of active ingredient (kg)	Number of DDDjps (1,000 s)	Number of DDDvets (1,000 s)**	TDjps	TDvets**	Weight of active ingredient (kg)	Number of DDDjps (1,000 s)	TDjps	Weight of active ingredient (kg)	Number of DDDjps (1,000 s)	Number of DDDvets (1,000 s)	TDjps	TDvets
Tetracyclines	27,489	834,869	908,122	3.02	3.28	173	5,528	0.02	27,316	829,341	902,594	3	3.26
Amphenicols	1,695	53,584	37,115	0.19	0.13	0	0	0	1,695	53,584	37,115	0.19	0.13
Penicillins	11,964	775,612	731,869	2.81	2.65	0	0	0	11,964	775,612	731,869	2.81	2.65
Sufonamides	4,541	102,922	121,701	0.37	0.44	4	136	0	4,537	102,785	121,565	0.37	0.44
Macrolides	10,301	174,966	244,150	0.63	0.88	0	0	0	10,301	174,966	244,150	0.63	0.88
Lincosamides	521	102,224	60,621	0.37	0.22	0	0	0	521	102,224	60,621	0.37	0.22
Aminoglycosides	7,764	320,156	320,156	1.16	1.16	690	17,855	0.06	7,074	302,300	302,300	1.09	1.09
Pleuromutilins	0	0	0	0	0	0	0	0	0	0	0	0	0
Cephalosporins	0	0	0	0	0	0	0	0	0	0	0	0	0
Trimethoprim	2,000	300,580	299,269	1.09	1.08	4	697	0	1,996	299,883	298,572	1.08	1.08
Polymyxins	606	37,893	118,881	0.14	0.43	0	0	0	606	37,893	118,881	0.14	0.43
Quinolones	2,892	245,042	264,056	0.89	0.96	0	0	0	2,892	245,042	264,056	0.89	0.96
Others	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	69,773	2,947,848	3,105,940	10.66	11.23	871	24,217	0.09	68,902	2,923,630	3,081,723	10.58	11.15

TDjps: Number of treatment days calculated using Japanese defined daily dose (DDDjp) values. TDvets: Number of treatment days calculated using European defined daily dose (DDDvet) values. * The absence of DDDvet values for parenteral products did not allow calculation of the number of DDDvets and the number of treatment days using DDDvet values (TDvets). **The total number of DDDvets and TDvets were calculated assuming that the nomber of DDDvets is the same as that of DDDjps for each parenteral antimicrobial class.

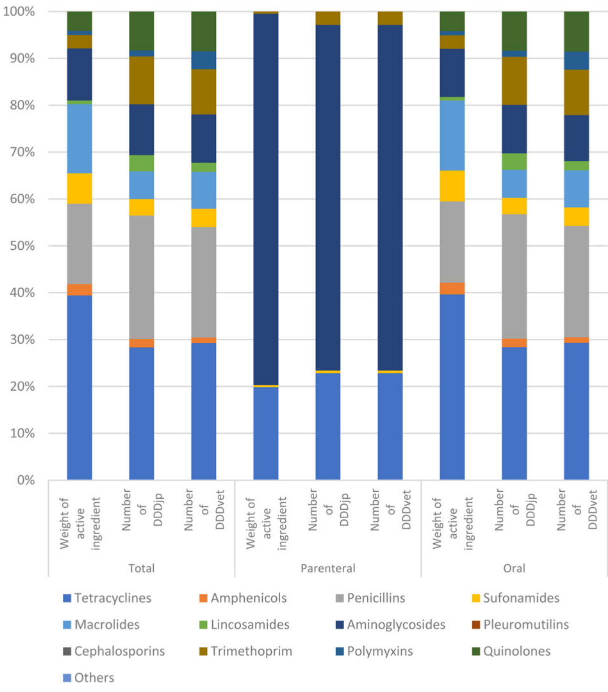

Fig. 5. Relative distribution of antimicrobial sales in broilers in Japan in 2019 showing different antimicrobial classes according to administration route and metric. DDDjp: Japanese defined daily dose; DDDvet: defined daily dose assigned by European Medicines Agency.

DISCUSSION

This study is the first attempt to have quantified the number of DDDs and TDs based on the weight of active ingredient sold for use in dairy cattle, beef cattle and broilers in Japan.

In interpreting the results, one should keep in mind that the number of DDDs and TDs only indicate the theoretical amount of biomass and the number of days that animals are subjected to treatment in a year respectively assuming that the antimicrobial products are used in a target animal of average weight at treatment according to the dosage specified in the summary of product characteristics. Under-dosing, over-dosing and disparity between the actual body weight and the standardized body weight could alter the results.

Our results revealed that regardless of the metrics used, tetracyclines and penicillins are the two most commonly used antimicrobial classes in all species. However, depending on the administration route, there were variations in the commonly used antimicrobials: aminoglycosides and cephalosporins are commonly used injection antimicrobials in dairy cattle; cephalosporins are dominantly used intramammary antimicrobials in dairy cattle; and aminoglycosides are dominantly used injection antimicrobials in broilers. With regard to relative distribution of antimicrobial sales by administration route, antimicrobials were administered mostly orally in all species in terms of the weight of active ingredient, while in terms of the number of DDDs and TDs, antimicrobials were administered mostly intramammarily in dairy cattle, by injection in beef cattle and orally in broilers.

Our results also revealed that the antimicrobial use in dairy cattle, beef cattle and broilers was much smaller than that in pigs in Japan regardless of the metrics used for calculation. Our previous study quantifying the antimicrobial sales in pigs [1] revealed that total number of DDDjps in pigs was 77,378 million kg·day, while in the current study, the numbers of DDDjps sold for use in dairy cattle, beef cattle and broilers were calculated to be 8,262, 3,928 and 2,948 million kg·days, 9.4, 19.7 and 26.2 times less than the sales in pigs, respectively. This magnitude of difference is more or less the same even if other metrics are used for calculation. This finding reconfirms that pigs are the heaviest antimicrobial user among food-producing animals in Japan.

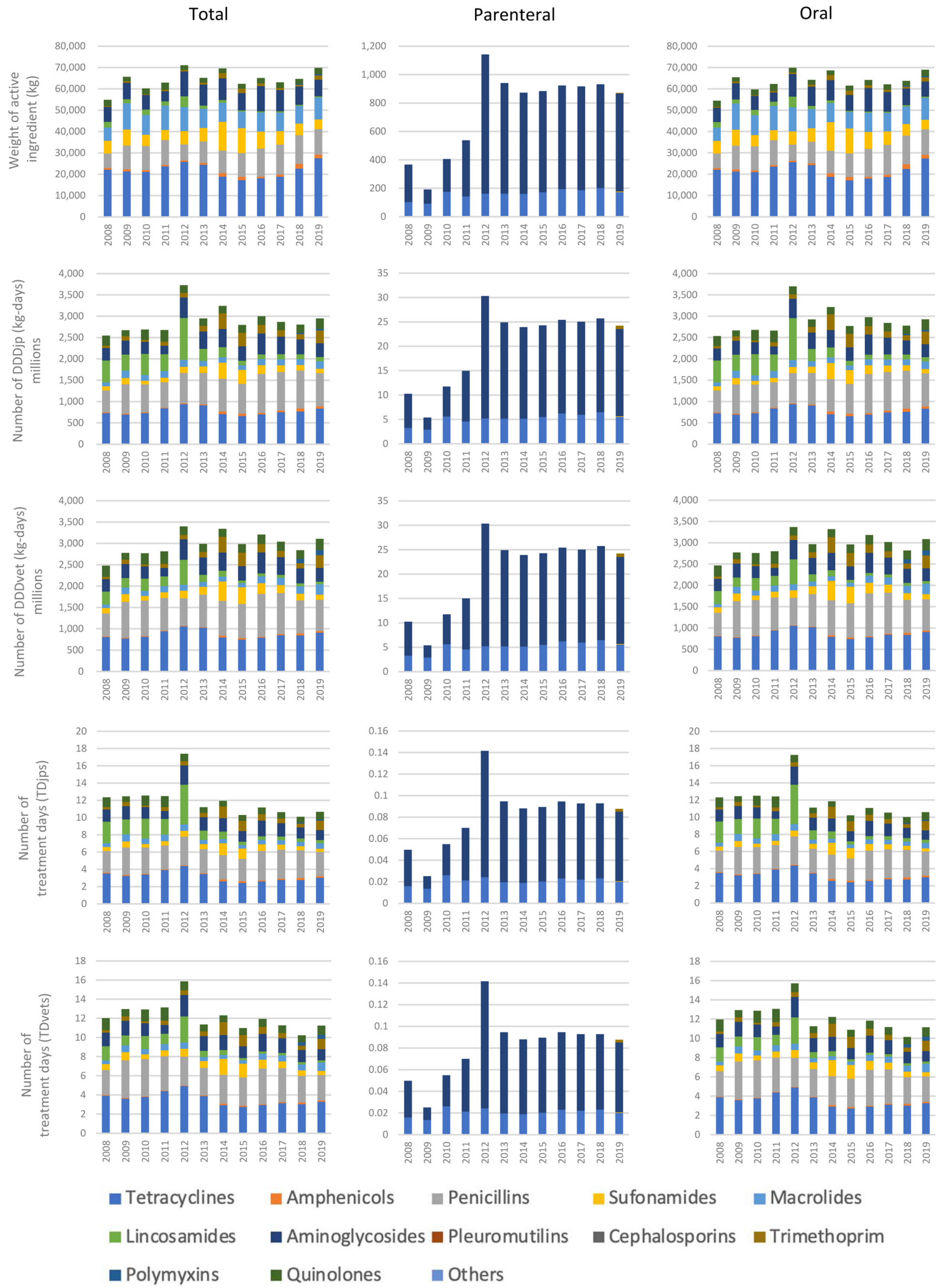

Fig. 6. Evolution of antimicrobial sales for use in broilers in Japan from 2008 to 2019 quantified using different metrics for different administration routes. DDDjp: Japanese defined daily dose; DDDvet: defined daily dose assigned by European Medicines Agency.

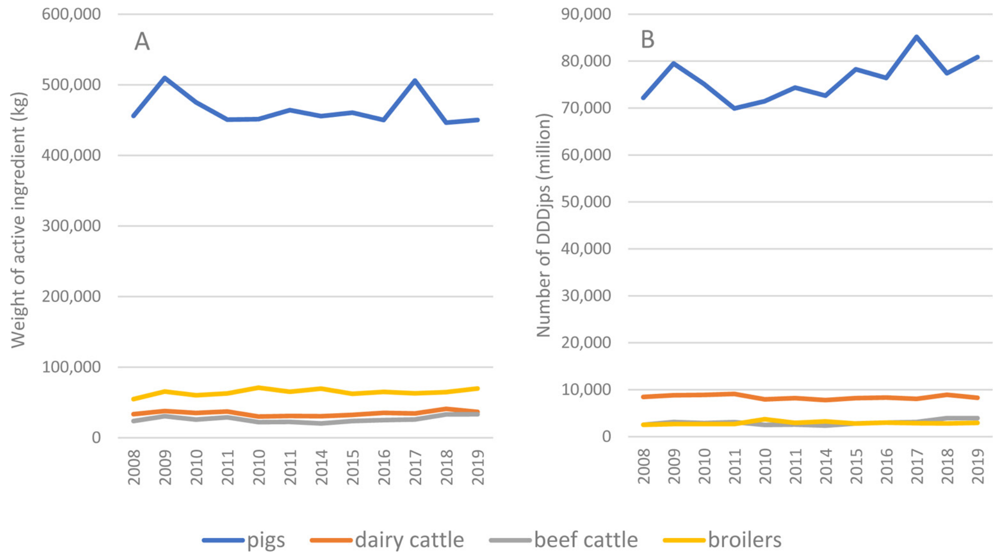

Fig. 7. Evolution of antimicrobial sales for use in dairy cattle, beef cattle, pigs and broilers in term of the weight of active ingredient **(A)** and the number of DDDjps **(B)** from 2008 to 2019. DDDjp: Japanese defined daily dose.

In the Netherlands, $DDDA_{NAT}$, a dosage-based indicator is used to monitor antimicrobial use at national level. The TDs used in this study is similar to $DDDA_{NAT}$ in the sense that they both present the theoretical number of days of treatment that an animal is subjected to in a year. The TDs calculated in this study for broilers (10.66 days in 2019) was comparable with the $DDDA_{NAT}$ (9.9 days in 2019), while that calculated for dairy cattle in Japan (15.5 days in 2019) was 5.2-fold larger than $DDDA_{NAT}$ (2.9 days in 2019) [16]. A study conducted in Belgium analyzing antimicrobial use on several dairy herds in Flanders revealed the average Antimicrobial Treatment Incidence (ATI) of 20.8 over the years from 2012 to 2013 [20]. ATI is a dosage-based indicator, presenting the number of animals subjected to treatment per 1,000 animals per day [20]. ATI of 20.78 corresponds to TDs of 7.5, indicating that the antimicrobial use in dairy cattle in Japan is twice as high as that in Flanders. A similar study was conducted in Brazil, which calculated antimicrobial usage for the treatment of clinical mastitis in dairy herds to be 21.9 using ATI [22]. Although not totally comparable, since our study included antimicrobials used for treatment of not only clinical but also other types of mastitis, the antimicrobial use in dairy cattle in Japan for mastitis treatment is more or less the same with that in Brazil.

As in our previous study that quantified the number of DDDs for antimicrobial agents for use in pigs [1], the relative distribution of different antimicrobial classes differed between the metrics used. Some antimicrobial classes with larger proportions than others when calculated with one metric had smaller proportions when calculated with other metrics. Especially tetracyclines for oral use in broilers and sulfonamides for oral use in cattle had larger DDD values than other antimicrobial classes, resulting in that their proportions to become larger when calculated in the weight of active ingredient than when dosage-based metrics were used. Contrarily, sales amount of cephalosporins for parenteral use in dairy cattle, trimethoprim for oral use in cattle and quinolones for parenteral use in beef cattle had larger proportions when calculated with dosage-based metrics than when calculated using a weight-based metric. Furthermore, some years experienced a remarkable decrease in antimicrobial use when calculated with weight-based metric while they saw a modest decrease when calculated using dosage-based metrics. For example, antimicrobials sold for parenteral use in beef cattle saw a decrease from 2008 to 2014 more remarkable in terms of the weight of active ingredient than in terms of the number of DDDjps and other metrics. This might have resulted from the sales of antimicrobials with small DDD values and high potency replacing the sales of antimicrobials with large DDD values and low potency during these years. This indicates the need for dosage-based metrics that reflects selection pressure taking account of potencies of different antimicrobial agents.

Potential factors that might affect the changes of antimicrobial use between years include epidemiological change of diseases that require the use of antimicrobials for their treatment and prevention; change of antimicrobial resistance in bacteria causative of diseases; approval of new antimicrobial products or withdrawal of existing products; introduction of new regulations on the use of antimicrobials; and errors made when the manufacturer reported the sales data to the Ministry of Agriculture, Forestry and Fisheries regarding the estimated relative distribution between species. However, no sufficient information is available to identify any of these factors as culprit of the above-mentioned temporal changes.

Our results revealed that the total number of DDDs and TDs were larger when calculated using DDDjp values than when calculated using DDDvet values. The total numbers of DDDs and TDs were slightly larger for broilers but significantly larger for cattle when calculated using DDDjp values than when calculated using DDDvet values. This is because DDDjp values and DDDvet values had similar values in broilers while most DDDjp values for products for use in cattle were larger than corresponding DDDvet values. For instance, the number of DDDs for macrolides sold for use in beef cattle was 3.14 fold larger when calculated using DDDjp values than when calculated using DDDvet values. Tulathromycin for parenteral use was responsible for this as its DDDjp value (2.5 mg/kg/day) was eight fold larger than its DDDvet value (0.3 mg/kg/day). Moreover, considering that Japanese veterinarians and farmers are likely to conform to Japanese doses rather than European doses, our results indicate the need for using DDDjp values over DDDvet values.

In terms of the weight of active ingredient, antimicrobials for intramammary and intrauterine use accounted for only 5.6% while they accounted for as much as 48.9% in terms of the number of DDDjps and TDs. This is because the DDD values of intramammary and intrauterine products are mostly much smaller than those of parenteral and oral products. The DDDjp values for intramammary products for lactating cows and intrauterine products that we used in this study were assigned by dividing the daily dose per teat by 635 kg. The DDDjp values for intramammary products for dry cows were assigned by multiplying the course dose per teat by four (number of teats per cow) and dividing it by 635 kg and an assumed long-acting factor of four days [21], following the Dutch way of assigning DDD values. In Germany and Canada, long-acting factors of seven and ten days are used respectively to assign DDD values for antimicrobial products for dry cow treatment [9]. In making international comparisons, one should keep in mind that not only the difference in dosing recommendations but also the choice of long-acting factors used to assign DDD values for dry cow products, because these factors have a non-negligible impact on the calculated results.

Despite these caveats with regard to DDD values and dose-based indicators as mentioned above, our results revealed differences in the numbers of DDDs and TDs and relative distributions by antimicrobial class between when calculated using DDDjp and DDDvet values, indicating the need for using the DDDjp values in monitoring the antimicrobial use in Japan.

POTENTIAL CONFLICTS OF INTEREST. The authors declare no conflicts of interest.

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