1 Establishing defined daily doses (DDDs) for antimicrobial agents used for pigs,
2 cattle and poultry in Japan and comparing them with European DDD values

3

4 Kyoko Fujimoto¹, Mai Kawasaki¹, Reiko Abe¹, Takashi Yokoyama¹, Takeshi Haga²
 5 and Katsuaki Sugiura^{1,*}

6

7 ¹ Department of Global Agricultural Sciences, Graduate School of Agricultural and
 8 Life Sciences, the University of Tokyo, Tokyo 113-8657 Japan

9 ² Department of Veterinary Medical Sciences, Graduate School of Agricultural and
 10 Life Sciences, the University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, 113-8657

11

12 *Corresponding author

13 E-mail address: aksugiur@mail.ecc.u-tokyo.ac.jp

14

15 **Abstract**

16 Monitoring of antimicrobial use is essential to manage the development and selection
 17 of antimicrobial resistance. A variety of indicators has become available to monitor
 18 antimicrobial use in human and animal medicine. One of them is an indicator based
 19 on defined daily dose (DDD). By using the number of DDDs used and normalizing it
 20 by the population at risk of being treated in a defined period, one can estimate the
 21 number of treatment days with antimicrobial agents in a population. For veterinary
 22 medicine, the European Medicines Agency (EMA) has published the European values
 23 of DDD (DDDvet) for food-producing animals. In this study, we defined Japanese
 24 defined daily doses for antimicrobial agents (DDDjp) using DDD values that we
 25 previously assigned for antimicrobial products approved for use in pigs, cattle and
 26 poultry in Japan and compared them with DDDvet values. For the comparison, the
 27 quotient of Japanese and European values (QDDD) was calculated and the effect of
 28 the administration route and the number of active substances contained in the
 29 preparation was investigated. A total of 59, 51 and 27 DDDjp values were defined for
 30 43, 32 and 25 antimicrobial agents using the data of 269, 195 and 131 products
 31 approved for use in pigs, cattle and poultry respectively. A comparison was possible
 32 for 44, 27 and 17 pairs of DDDjp and DDDvet values for antimicrobial agents used

33 for pigs, cattle and poultry respectively. The comparison showed median QDDD
34 value of 0.66 and 0.63 for antimicrobial agents used for pigs and cattle respectively
35 ($P < 0.01$), indicating that the Japanese daily doses are significantly lower than the
36 corresponding EMA values in these species. For the antimicrobial agents used for
37 poultry, no significant difference was observed between DDDjp and DDDvet values
38 with median QDDD value of 1.17. The difference between DDDvet and DDDjp
39 values and absence of DDDvet values for some antimicrobial agents marketed in
40 Japan indicate that DDDjp rather than DDDvet should be used as the basis for the
41 calculation of antimicrobial use monitoring in farm animals in Japan.

42

43 **Introduction**

44 The use of antimicrobial agents in food producing animals may lead to the
45 emergence and selection of resistant bacteria. The bacterial resistance arises through
46 complex mechanisms, normally through mutation and selection, or by acquiring from
47 other bacteria the genetic information that encodes resistance [1]. Therefore, reducing
48 the selection pressure by reducing antimicrobial usage is considered one of the
49 important strategies to decrease the resistance rate [1].

50 An important tool for the control and reduction of antimicrobial use in veterinary
51 medicine is the establishment of a monitoring system, which can be based on various
52 types of data collection [2]. In the EU, antimicrobial sales data are collected from
53 each member country and antimicrobial consumption in each member is calculated
54 and published in terms of milligrams of active ingredient sold per population
55 correction unit (mg/PCU). The authors have previously calculated the antimicrobial
56 usage in food-producing animals in Japan using the same indicator [3]. The
57 disadvantage of this monitoring system is that the different potencies of different
58 antimicrobial agents are not taken into account [4]. In human medicine the World
59 Health Organization (WHO) has determined an average daily maintenance dose for
60 the main indication for each active substance [5]. Using the daily doses and the

amount of an active ingredient used, the number of potential treatment days in a population can be estimated. This statistical value has been adapted to veterinary medicine and is the basis of the national antibiotic monitoring systems in several Scandinavian countries and the Netherlands [6, 7, 8].

A list of defined daily doses for the food-producing animals (DDDvet) has been available from the European Medicines Agency (EMA) since 2016 [9]. Dose data from nine EU member states were collected and average values for the daily doses of each active ingredient by administration route ("parenteral", "oral except premix" and "premix") and by species were calculated. The antimicrobial active ingredients were classified based on anatomical-therapeutic-chemical correspondences (ATCvet Code) [10].

In the hope to establish a monitoring system using an indicator based on daily dosage, the authors have previously assigned DDD values for 269, 195 and 131 veterinary antimicrobial products approved and marketed for use in pigs, cattle and poultry in Japan [11, 12].

The aim of the present study was to define Japanese daily doses (DDDjp) for each antimicrobial agent (active ingredient) based on these DDD values assigned for products and to compare them with the values of the EMA.

79

80 **Materials and Methods**

81 **Defining Japanese DDD values for antimicrobial agents used** 82 **for pigs, cattle and poultry in Japan (DDDjp)**

83 The DDDjp values were calculated using the DDD values that we previously
84 assigned for 259, 195 and 131 veterinary antimicrobial products approved and
85 marketed for use in pigs, cattle and poultry respectively in Japan [11, 12]. In our
86 previous study, the DDD values for antimicrobial products other than intramammary
87 and intrauterine products were assigned by species and by kg animal, using the
88 principles developed by the European Medicines Agency [13]. The DDD values were
89 assigned by kg animal by dividing the daily dose by 635kg (average weight of dairy
90 cow in Japan) for intramammary products for lactating cows and intrauterine
91 products, and by multiplying the dose by 4 (number of teats) and dividing it by 635kg
92 and an assumed long acting factor of 10 days for products for dry cows [12].

93 In the current study, the DDDjp values were calculated by averaging the DDD values
94 of products if there are two or more products containing the same antimicrobial agent:

$$95 \quad \text{DDDjp for antimicrobial agent a (mg/kg)} = \frac{\sum_{i=1}^n \text{DDD}_i}{n}$$

96 where DDD_i is the DDD value (mg/kg) of antimicrobial product i containing

antimicrobial agent a, and n is the number of products containing antimicrobial agent a. For those antimicrobial agents that are used as active ingredient in products for two or more administration routes, DDD values were assigned separately by administration route. Likewise, for those that are used both in single substance and combination products, DDD values were assigned separately by the number of active ingredients contained in the preparation. In other words, the average (arithmetic mean) of all DDD values of products for each combination of species, antimicrobial agent, administration route and the number of substances in the product (single substance or combination product) was used to assign DDD_{jp} – e.g. pig/benzylpenicillin/injectable/single substance.

Comparison of DDD_{jp} and DDD_{vet} values

For the comparison with the values of the EMA, the quotient of the daily doses (QDDD) was formed from Japanese and EMA values:

$$QDDD = \frac{DDD_{jp}}{DDD_{vet}}$$

If the quotient shows a value of one, it means that the Japanese dose and the EMA dose are the same. Quotients greater than one mean that the Japanese dosages are higher and values below one mean that they are lower. If there was no EMA value

for an active ingredient, the antimicrobial agent was excluded from the comparison.

The effect of the number of active ingredients contained in the product and the administration route on the comparison was examined.

Statistical analysis

The statistical analysis was carried out to verify a deviation of QDDD between administration routes and number of active ingredients with BellCurve for Excel version 3.20 (Social Survey Research Information Co., Ltd.). A P-value ≤ 0.05 was set as the significance level. The data were checked for normal distribution by Shapiro tests. The difference between DDDvet and DDDjp values was examined using the Wilcoxon test for paired samples. The effects of the administration routes and the number of active ingredients in the product were examined using a Mann-Whitney U test.

RESULTS

Distribution of antimicrobial products approved for use in pigs in Japan

A total of 60, 54 and 27 DDDjp values were defined for 43, 32 and 25 antimicrobial agents using the data of 259, 195 and 131 products approved for use in

pigs, cattle and poultry respectively. The distribution of the products according to the administration route and the number of active substances in the preparation is shown in Tables 1, 2 and 3. A complete list of the antimicrobials for which DDDjp values were defined are shown in Table 4.

Table 1

Distribution of the antimicrobial products approved for use in pigs in Japan by administration route and the number of active ingredient contained

Type of product	Administration route			Total
	Injection	Oral	Topical	
Single substance product	75	133	1	209
Combination product	18	42	0	60
Total	93	175	1	269

Table 2

Distribution of the antimicrobial products approved for use in cattle in Japan by administration route and the number of active ingredients contained

Type of product	Administration route				Total
	Injection	Oral	Intrauterine	Intramammary	
Single substance product	96	51	0	18	165

Combination product	12	9	2	7	30
Total	108	60	2	25	195

145

146 **Table 3**

147 **Distribution of the antimicrobial products approved for use in poultry in Japan**

148 **by administration route and the number of active ingredients contained**

Type of product	Administration route		Total
	Injection	Oral	
Single substance product	18	87	105
Combination product	0	26	26
Total	18	113	131

149

150 **Table 4**

151 **Japanese DDD values (DDDjp) defined in this study for antimicrobial agents used for pigs, cattle and poultry in Japan and**
 152 **corresponding DDD values (DDDvet) defined by the European Medicines Agency**

Antimicrobial class	Antimicrobial agent (active ingredient)	Product type	Administration route	DDDvet	DDDjp	Number of products
Antimicrobial agents used for pigs						
Tetracyclines	Oxytetracycline	Single substance product	Injection	7.5	6.5	2
Amphenicols	Thiamphenicol	Single substance product	Injection	75.0	20.0	2
	Florfenicol	Single substance product	Injection	9.5	5.0	4
Penicillins	Ampicillin	Single substance product	Injection	12.0	6.5	7
	Amoxicillin	Single substance product	Injection	8.9	7.5	1
	Procaine Benzylpenicillin	Single substance product	Injection	12.0	2.7	8
	Procaine Bensylpenicillin	Combination product	Injection	5.4	7.2	6
Cefalosporins	Ceftiofur	Single substance product	Injection	3.0	2.5	5
	Cefquinome	Single substance product	Injection	1.9	1.5	2
	Sulfadimethoxine	Single substance product	Injection	30.0	60.0	2
Sulfonamides	Sulfamonomethoxine	Single substance product	Injection		70.0	1
	Sulfadoxine	Combination product	Injection	14.0	30.0	3
	Trimethoprim	Combination product	Injection	3.0	6.0	3

Trimethoprim	Erythromycin	Single substance product	Injection	21.0	4.5	0
Macrolides	Tylosin	Single substance product	Injection	13.0	6.0	3
	Tulathromycin	Single substance product	Injection		2.5	4
Lincosamides	Lincomycin	Single substance product	Injection	10.0	7.5	4
Aminoglycosides	Dihydrostreptomycin	Single substance product	Injection	20.0	60.0	2
	Dihydrostreptomycin	Combination product	Injection		15.0	6
	Kanamycin	Single substance product	Injection	28.0	15.0	11
	Kanamycin (topical)	Single substance product	局所		110.0	1
Quinolones	Enrofloxacin	Single substance product	Injection	3.4	2.6	8
	Danofloxacin	Single substance product	Injection	1.2	1.3	1
	Marbofloxacin	Single substance product	Injection	2.0	2.0	3
	Orbifloxacin	Single substance product	Injection		3.8	3
Pleuromutilins	Tiamulin	Single substance product	Injection	12.0	10.0	2
Tetracyclines	Doxycycline	Single substance product	Oral	11.0	9.0	10
	Chlortetracycline	Single substance product	Oral	31.0	10.8	6
	Chlortetracycline	Combination product	Oral		6.0	2
	Oxytetracycline	Single substance product	Oral	26.0	9.4	7
	Oxytetracycline	Combination product	Oral		7.0	1
Amphenicoles	Thianphenicol	Single substance product	Oral	35.0	5.0	7
	Florfenicol	Single substance product	Oral	10.0	1.5	18

Penicillins	Ampicillin	Single substance product	Oral	30.0	8.0	8
	Amoxicillin	Single substance product	Oral	17.0	6.5	8
	Benzylpenicillin	Combination product	Oral		0.8	5
Sulfonamides	Sulfadimethoxine	Single substance product	Oral	48.0	54.0	2
	Sulfadimethoxine	Combination product	Oral	24.0	28.8	2
	Sulfamonomethoxine	Single substance product	Oral		40.0	7
	Sulfamonomethoxine	Combination product	Oral	9.4	8.1	4
	Sulfamethoxine	Combination product	Oral	20.0	4.7	7
	Sulfadimidine	Combination product	Oral	23.0	6.0	2
Trimethoprim	Trimethoprim	Combination product	Oral	4.7	1.4	9
	Ormethoprim	Combination product	Oral		2.7	4
Macrolides	Tylosin	Single substance product	Oral	12.0	11.3	13
	Tilmicosin	Single substance product	Oral	15.0	5.0	9
	Tylvalosin	Single substance product	Oral	3.6	1.4	2
	Mirosamycin	Single substance product	Oral		2.5	0
Lincosamides	Lincomycin	Single substance product	Oral	7.6	4.2	6
Aminoglycosides	Streptomycin	Single substance product	Oral		20.0	1
	Streptomycin	Combination product	Oral		4.2	3
	Gentamicin	Single substance product	Oral	1.4	0.6	1
	Kanamycin	Combination product	Oral		4.2	2

	Apramycin	Single substance product	Oral	9.0	4.0	1
	Fragiomycin	Combination product	Oral		4.9	1
Fluoroquinolones	Norfloxacin	Single substance product	Oral		7.5	1
	Oxolinic acid	Single substance product	Oral	26.0	20.0	3
Other quinolones	Tiamulin	Single substance product	Oral	9.7	6.4	15
Pleuromutilins	Valnemulin	Single substance product	Oral	5.3	2.6	1
Polymyxins	Colistin	Single substance product	Oral	5.0	4.8	7
Total for pigs						269
Antimicrobial agents used for cattle						
Tetracyclines	Oxytetracycline	Single substance product	Injection	6.5	6.0	7
Amphenicols	Thiamphenicol	Single substance product	Injection		20.0	2
	Florfenicol	Single substance product	Injection	13.0	10.0	9
Penicillins	Ampicillin	Single substance product	Injection	11.0	6.2	14
	Amoxicillin	Single substance product	Injection	8.3	7.5	1
	Benzylpenicillin	Single substance product	Injection	14.0	2.1	1
	Procaine benzylpenicillin	Single substance product	Injection	13.0	7.5	8
	Procaine benzylpenicillin	Combination product	Injection		4.2	6
	Aspoxicillin	Single substance product	Injection		6.3	0
Cefalosporins	Cefazolin	Single substance product	Injection		5.0	4
	Ceftiofur	Single substance product	Injection	1.0	2.3	5

	Cefquinome	Single substance product	Injection	1.5	1.0	2
Sulfonamides	Sulfadimethoxine	Single substance product	Injection	30.0	35.0	2
	Sulfamonomethoxine	Single substance product	Injection		25.0	1
Macrolides	Tylosin	Single substance product	Injection	13.0	7.0	3
	Tulathromycin	Single substance product	Injection	0.3	2.5	3
	Tilmicosin	Single substance product	Injection	4.0	10.0	5
Aminoglycosides	Dihydrostreptomycin	Single substance product	Injection	25.0	15.0	3
	Dihydrostreptomycin	Combination product	Injection		8.8	6
	Kanamycin	Single substance product	Injection	15.0	7.5	11
Quinolones	Enrofloxacin	Single substance product	Injection	4.2	4.2	8
	Danofloxacin	Single substance product	Injection		1.3	1
	Marbofloxacin	Single substance product	Injection	3.6	2.0	3
	Orbifloxacin	Single substance product	Injection		3.8	3
Others	Fosfomycin	Single substance product	Injection		15.0	1
Tetracyclines	Chlortetracycline	Single substance product	Oral	22.0	12.5	6
	Oxytetracycline	Single substance product	Oral	20.0	8.1	7
	Oxytetracycline	Combination product	Oral		12.5	1
Penicillins	Ampicillin	Single substance product	Oral	29.0	8.0	8
	Amoxicillin	Single substance product	Oral	20.0	6.5	8
Sulfonamides	Sulfamonomethoxine	Single substance product	Oral		45.0	8

	Sulfamonomethoxine	Combination product	Oral		11.3	2
Trimethoprim	Ormethoprim	Combination product	Oral		3.8	2
Macrolides	Tylosin	Single substance product	Oral	41.0	30.8	1
	Tilmicosin	Single substance product	Oral	21.0	14.1	2
Aminoglycosides	Streptomycin	Single substance product	Oral	70.0	20.0	1
	Gentamicin	Single substance product	Oral	7.0	2.0	1
	Fragiomyacin	Combination product	Oral	7.4	8.8	1
Fluoroquinolones	Enrofloxacin	Single substance product	Oral	4.7	3.8	1
Other quinolones	Oxolinic acid	Single substance product	Oral	17.0	15.0	4
Polymyxins	Colistin	Single substance product	Oral	4.8	3.5	2
Others	Fosfomycin	Single substance product	Oral		30.0	2
Penicillins	Procaine benzylpenicillin	Combination product	Intrauterine		0.2	1
Aminoglycosides	Dihydrostreptomycin	Combination product	Intrauterine		0.3	1
Cephalosporins	Cefazolin	Single substance product	Intramammary		0.3	9
	Cefalonium	Single substance product	Intramammary		0.2	3
	Cefuroxime	Single substance product	Intramammary		0.6	2
Tetracyclines	Oxytetracycline	Single substance product	Intramammary		1.1	1
Penicillins	Procaine benzylpenicillin	Combination product	Intramammary		0.4	4
	Dicloxacillin	Single substance product	Intramammary		0.3	2
Aminoglycosides	Dihydrostreptomycin	Combination product	Intramammary		0.6	2

	Kanamycin	Combination product	Intramammary		0.5	1
	Fradiomycin	Combination product	Intramammary		0.5	1
Lincosamides	Pirlimycin	Single substance product	Intramammary		0.1	1
Total for cattle						196
Antimicrobial agents used for poultry						
Tetracyclines	Oxytetracycline	Single substance product	Injection		31.3	5
Aminoglycosides	Dihydrostreptomycin	Single substance product	Injection		62.5	2
	Kanamycin	Single substance product	Injection		37.5	11
Tetracyclines	Doxycycline	Single substance product	Oral	15.0	17.3	12
	Chlortetracycline	Single substance product	Oral	30.0	35.1	6
	Oxytetracycline	Single substance product	Oral	39.0	40.7	7
Amphenicoles	Thianphenicol	Single substance product	Oral	55.0	39.0	7
	Florfenicol	Single substance product	Oral	30.0	20.0	1
Penicillins	Amoxicillin	Single substance product	Oral	16.0	30.0	8
	Ampicillin	Single substance product	Oral	108.0	16.3	8
	Procaine benzylpenicillin	Combination product	Oral		4.7	5
Sulfonamides	Sulfadimethoxine	Single substance product	Oral	65.0	106.3	2
	Sulfadimethoxine	Combination product	Oral	31.0	56.2	2
	Sulfamonomethoxine	Single substance product	Oral		97.5	7
	Sulfamonomethoxine	Combination product	Oral	9.5	31.9	4

	Sulfamethoxazole	Combination product	Oral	27.0	32.5	2
Trimethoprim	Trimethoprim	Combination product	Oral	6.4	6.4	4
	Ormethoprim	Combination product	Oral		10.5	4
Macrolides	Tylosin	Single substance product	Oral	81.0	78.9	13
	Tylvalosin	Single substance product	Oral	25.0	47.6	3
Lincosamides	Lincomycin	Single substance product	Oral	8.6	5.1	6
Aminoglycosides	Streptomycin	Combination product	Oral		23.4	3
	Kanamycin	Combination product	Oral		23.4	2
Fluoroquinolones	Norfloxacin	Single substance product	Oral		20.0	1
	Enrofloxacin	Single substance product	Oral	10.0	11.5	1
	Ofloxacin	Single substance product	Oral		7.5	1
Other quinolones	Oxolinic acid	Single substance product	Oral	20.0	39.7	4
Total for poultry						131

153 DDDvet: DDD values in mg/kg/day defined by the European Medicines Agency (EMA)

154 DDDjp: DDD values in mg/kg/day defined in this study using DDD values of antimicrobial products approved and marketed for use in Japan

155

Comparison of the DDDjp values with DDDvet values for antimicrobial agents for use in pigs

A comparison of 44 pairs of DDDjp and DDDvet values of antimicrobial agents for use in pigs was possible. The distribution of the logarithmic quotients of daily doses is shown in Figure 1A. A total of 27 compared values showed deviations of more than 50% (Fig. 1A). A significant difference between the DDDvet and DDDjp values was observed for antimicrobial agents used for pigs ($P < 0.01$) with the median QDDD value of 0.66.

The administration route showed a significant difference ($P = 0.011$) in terms of the level of the deviations between the DDDjp and DDDvet values (Table 5). In comparison with the guideline values of the EMA, the injection solutions with the active substances kanamycin and ampicillin showed lower daily doses with QDDD of 0.54 and 0.54 respectively. Injection solution with the active substance benzylpenicillin showed lower daily doses (QDDD=0.23) in single substance products but showed higher daily doses (QDDD=1.33) in combination products. With antimicrobial agents for oral administration, florfenicol, trimethoprim and tiamulin were approved in Japan with lower daily doses with QDDD of 0.15, 0.31 and 0.66 respectively (Table 6).

The number of active substances contained in a veterinary medicinal product ($P < 0.01$) did not show a significant difference in terms of the level of the deviations between the daily doses DDDjp and DDDvet (Table 5).

Fig 1. Comparison of the DDDjp values of antimicrobial agents approved in Japan with the corresponding values of the European Medicines Agency. Bars indicate an antimicrobial agent approved for use in pigs (A), cattle (B) and poultry (C) for which both DDDjp and DDDvet values are available with QDDD values in ascending order. The red, pink, blue and light blue bars are injection/single substance, injection/combination, oral/single and oral/combination respectively.

Table 5

Statistical evaluation of the calculated quotients QDDD in relation to administration routes and the number of active ingredients contained in the preparation (Mann-Whitney U Test)

		Median QDDD	Statistical Significance
Antimicrobial agents used for pigs			
Administration route			
	Injection	0.833	Significant (P=0.010)
	Oral	0.444	
Number of substances			
	Single substance	0.595	Not significant (P=0.14)
	Combination	1.031	
Antimicrobial agents used for cattle			
Administration route			
	Injection	0.718	Not significant (P=0.18)
	Oral	0.568	
Number of substances			
	Single substance	0.633	- *
	Combination	1.182	
Antimicrobial agents used for poultry			

Administration route			
	Injection	- **	- **
	Oral	1.153	
Number of substances			
	Single substance	1.150	Not significant (P=0.16)
	Combination	1.508	

DDD: Defined Daily Doses

Median QDDD: calculated quotient of Japanese daily doses and the corresponding values of the European Medicines Agency

*: Statistical evaluation was not possible because there was only one combination antimicrobial agent for which DDDvet and DDDjp values were available.

**: Median QDDD value was not available and statistical evaluation was not possible because there was no antimicrobial agent for injection for which DDDvet and DDDjp values were available.

Table 6

Average daily doses (DDDjp) of the most frequently approved antimicrobial agents (divided by administration routes) in the pig, cattle and poultry sector in Japan and their comparison with the values of the European Medicines Agency (DDDvet) based on calculated quotients (QDDD)

Administration route	Antimicrobial agent (active ingredient)	Number of substances	DDDjp (Number of products approved)	DDDvet	QDDD
Antimicrobial agents used for pigs					
Injection	Kanamycin	single substance	15.0 (11)	28.0	0.54
	Procaine benzylpenicillin	single substance	2.7 (8)	12.0	0.23
	Enrofloxacin	single substance	2.6 (8)	3.4	0.76
	Ampicillin	single substance	6.5 (7)	12.0	0.54
	Procaine benzylpenicillin	combination	7.2 (6)	5.4	1.33
Oral	Florfenicol	single substance	1.5 (18)	10.0	0.15
	Tiamulin	single substance	6.4 (15)	9.7	0.66
	Tylosin	single substance	14.0 (13)	12.0	1.17

	Doxycycline	single substance	9.0 (10)	11.0	0.82
	Trimethoprim	combination	1.4 (9)	4.7	0.31
Antimicrobial agents used for cattle					
Injection	Ampicillin	single substance	6.2 (14)	11.0	0.56
	Kanamycin	single substance	7.5 (11)	15.0	0.50
	Florfenicol	single substance	10.0 (9)	13.0	0.77
	Procaine benzylpenicillin	single substance	7.5 (8)	13.0	0.58
	Enrofloxacin	single substance	4.2 (8)	4.2	1.00
Oral	Ampicillin	single substance	8.0 (8)	29.0	0.28
	Amoxicillin	single substance	6.5 (8)	20.0	0.33
	Oxytetracycline	single substance	8.1 (7)	20.0	0.41
	Chlortetracycline	single substance	12.5 (6)	22.0	0.57
	Oxolinic acid	single substance	15.0 (4)	17.0	0.88
Antimicrobial agents used for poultry					
Oral	Tylosin	single substance	78.9 (13)	81.0	0.97
	Doxycycline	single substance	17.3 (12)	15.0	1.15
	Ampicillin	single substance	16.3 (8)	108.0	0.15
	Amoxicillin	single substance	30.0 (8)	16.0	1.88
	Oxytetracycline	single substance	40.7 (7)	39.0	1.04

DDDjp: defined daily doses of the active ingredient used in pigs in Japan established in this study.
 DDDvet: defined daily doses of the active ingredient used in pig in Europe established by the European Medicines Agency.
 QDDD: calculated quotient of DDDjp/DDDvet.

Comparison of the DDDjp values with DDDvet values for antimicrobial agents for use in cattle

A comparison of 27 pairs of DDDjp and DDDvet values of antimicrobial agents for use in cattle was possible. The distribution of the logarithmic quotients of daily doses is shown in Figure 1B. A total of 10 compared values showed deviations of more than 50% (Fig. 1B). A significant difference between the DDDvet and DDDjp

values was observed for antimicrobial agents used for cattle ($P < 0.01$) with the median QDDD value of 0.63.

Neither the administration route nor the number of active substance contained in a veterinary medicinal product showed a significant difference in terms of the level of the deviations between the DDD_{jp} and DDD_{vet} values (Table 5). In comparison with the guideline values of the EMA, the injection solutions with the active substances ampicillin, kanamycin and procaine benzylpenicillin showed lower daily doses with QDDD of 0.56, 0.50 and 0.58 respectively. With antimicrobial agents for oral administration, ampicillin, amoxycillin and oxytetracycline were approved in Japan with lower daily doses with QDDD of 0.28, 0.33 and 0.41 respectively (Table 6).

Comparison of the DDD_{jp} values with DDD_{vet} values for antimicrobial agents for use in poultry

A comparison of 17 pairs of DDD_{jp} and DDD_{vet} values of antimicrobial agents for use in poultry was possible. The distribution of the logarithmic quotients of daily and treatment dosages is shown in Figure 1C. A total of 5 compared values showed deviations of more than 50% (Fig. 1C). No statistically significant difference was observed between the DDD_{vet} and DDD_{jp} values with the median QDDD value of 1.17.

Neither the administration route nor the number of active substances contained in a veterinary medicinal product showed a significant difference in terms of the level of the deviations between the DDD_{jp} and DDD_{vet} values (Table 5). In comparison with the guideline values of the EMA, the oral solutions with the active substance

ampicillin showed lower daily dose with QDDD of 0.15 and amoxicillin with higher daily dose with QDDD of 1.88 (Table 6).

Discussion

The present study defined national daily dosages (DDDjp) for the first time for all antimicrobial agents used in products approved for use in pigs, cattle and poultry in Japan. A comparison with corresponding values of the EMA was possible for most antimicrobial agents. The comparison within this study shows that the medians of DDDjp and DDDvet values differ significantly, and that DDDjp values of some antimicrobial have considerable deviations from corresponding DDDvet values. Canada also found that in developing their country-specific DDD values, the majority of their DDD values were lower than their corresponding DDDvet values [14]. In a previous study conducted by Echtermann defining Swiss daily doses (DDDch), the difference between DDDch and DDDvet values was not as significant as between DDDjp and DDDvet values in the current study [15]. There are many reasons for the difference observed between DDDvet and DDDjp or DDD values in other non-European countries. One reason is that the EMA might have had a wider range of antimicrobial doses to work with due to the collection of antimicrobial agent doses from nine European countries [9, 13]. The different labelling regulations, different treatment indications and different husbandry practices might all contribute to the variations in DDDvet and DDDjp values. However, fully elucidating the reasons for these differences is beyond the scope of this study.

Furthermore, this study showed that DDDvets did not cover all the antimicrobial agents used in veterinary medicine in Japan. Although drawing conclusions from differences between assigned DDDjp and DDDvet values is difficult, the difference between DDDvet and DDDjp values and absence of DDDvet values for some antimicrobial agents marketed in Japan indicate that DDDjp rather than DDDvet should be used as the basis for the calculation of antimicrobial use monitoring in farm animals in Japan, assuming that DDDjp better reflects the actual dosage used in food-producing animals in Japan. This is a reasonable assumption considering that Japanese veterinarians are more likely to follow dosage instructions rather than European instructions when they treat pigs using antimicrobials marketed in Japan.

To determine if the use of DDDjp is really recommendable as the basis for the calculation of antimicrobial use on farms in Japan, application of DDDjp and DDDvet values for calculation of the numbers of DDDs for comparison using actual antimicrobial usage data on farms is indispensable, but this will be a subject of future studies.

Acknowledgements

This study was conducted as part of the research project on Regulatory research projects for food safety, animal health and plant protection (Grant number: JPJ008617.17935699. 1120) funded by the Ministry of Agriculture, Forestry and Fisheries of Japan.

References

1. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, Guerin PJ, Piddock, LJV. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet*. 2016; 387: 176–187.
2. AACTING-network. Description of Existing Monitoring Systems for Collection, Analysis, Benchmarking and Reporting of Farm-Level Veterinary Antimicrobial Usage-Version 1.4_2018-11-07. [Cited 2020 July 25] Available from: <https://aacting.org/monitoring-systems/>
3. Hosoi Y, Asai T, Koike R, Tsuyuki M, Sugiura K. Sales of veterinary antimicrobial agents for therapeutic use in food-producing animal species in Japan between 2005 and 2010. *Rev sci tech Off Int Epiz*. 2014; 33: 107-1015.
4. European Medicines Agency (EMA), 2012. Revised ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136456.pdf (accessed 25 May 2020)
5. WHO Collaborating Centre for Drug Statistics and Methodology, 2020. ATCvet Index 2020. [Cited 2020 July 25] Available from: <http://www.whocc.no/atcvet/atcvet/>
6. Grave K, Torren-Edo J, Muller A, Greko C, Moulin G, Mackay D, ESVAC-Group. Variations in the sales and sales patterns of veterinary antimicrobial agents in 25 European countries. *J Antimicrob Chemother*. 2014;

- 69: 2284-2291.
7. Jensen VF, Jacobsen E, Bager F. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. *Prev Vet Med.* 2004; 64: 201-215.
8. Netherlands Veterinary Institute (SDa). Usage of antibiotics in agricultural livestock in the Netherlands in 2017-Trends and benchmarking of livestock farms and veterinarians. [Cited 2020 July 25] Available from: <https://cdn.ipulse.nl/autoriteitdiergeneesmiddelen/userfiles/Publications/engels-def-rapportage-2017.pdf>
9. European Medicines Agency (EMA). Defined daily doses for animals (DDDvet) and defined course doses for animals (DCDvet). [Cited 2020 July 25] Available from: https://www.ema.europa.eu/en/documents/other/defined-daily-doses-animals-dddvet-defined-course-doses-animals-dcdvet-european-surveillance_en.pdf
10. WHO Collaborating Centre for Drug Statistics and Methodology, 2018. DDD: Definition and general considerations. [Cited 2020 July 25] Available from: www.whocc.no/ddd/definition_and_general_considera
11. Takagi H, Lei Z, Yamane I, Yamazaki H, Kure K, Sugiura K. Establishing DDD values for veterinary antimicrobial products in Japan for measuring antimicrobial use on pig farms. *Journal of Japanese Veterinary Medical Association* 2020; 73: 352-355
12. Fijimoto K, Shimizu H, Kikuchi M, Matsui T, Ito M, Hashimoto S et al. 2020. Establishing DDD values for veterinary antimicrobial products in Japan for measuring antimicrobial use on pig farms. *Journal of Japanese Veterinary Medical Association* (under review)

13. European Medicines Agency (EMA). Principles on assignment of defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet). [Cited 2020 September 25] Available from : https://www.ema.europa.eu/en/documents/scientific-guideline/principles-assignment-defined-daily-dose-animals-dddvet-defined-course-dose-animals-dcdvet_en.pdf
14. Bosman AL, Loest D, Carson CA, Agunos A, Collineau L, Léger DF. Developing Canadian Defined Daily Doses for Animals: A Metric to Quantify Antimicrobial Use. Front Vet Sci. 2019 Jul 17;6:220. doi: 10.3389/fvets.2019.00220
15. Echtermann T, Muentener C, Sidler X, Kümmerlen D. Antimicrobial Drug Consumption on Swiss Pig Farms: A Comparison of Swiss and European Defined Daily and Course Doses in the Field. Front Vet Sci. 2019; 6: 1-11.

Figure1

Comparison of the DDDjp values of antimicrobial agents approved in Japan with the corresponding values of the European Medicines Agency. Bars indicate an antimicrobial agent approved for use in pigs (A), cattle (B) and poultry (C) for which both DDDjp and DDDvet values are available with QDDD values in ascending order. The red, pink, blue and light blue bars are injection/single substance, injection/combination, oral/single and oral/combination respectively.