Evaluation of antibiotic usage in swine reproduction farms in Umbria region based on the quantitative analysis of antimicrobial consumption

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Abstract

Antibiotic use in food-producing animals has considerable impact on public health, especially with respect to the development and spread of antibiotic resistance. Pigs represent one of the main species in which antibiotics are frequently used for different purposes. Surveillance of antibiotic consumption and dose appropriateness, through novel approaches based on *defined daily doses,* is strongly needed to assess farms' antibiotic risk, in terms of spread of antibiotic resistance and possibile presence of residues in meat. In this study, antibiotic consumption was monitored in 14 swine reproduction farms, together with managerial, structural, and health aspects. Most of the controlled farms (65%) were classified as *at medium antibiotic risk*, 21% at *high antibiotic risk*, and 14% at *low antibiotic risk*. Critical aspects of antibiotic administration concerned treatments for suckling and weaner piglets, oral antibiotic administration, treatment and diagnosis of gastroenteric infections, and use of critically important antimicrobials for human medicine, especially colistin. These aspects could be considered critical aspects of antibiotic use in *from-farrow-to-wean/finish* swine farms in the Umbria region and must be controlled to minimize risks. Even though a small number of farms in Umbria region are at high antibiotic risk, the risk of antibiotic resistance should be minimized, and management and biosecurity of the farms should be improved by extending the use of antimicrobial susceptibility tests and optimizing the diagnostic methods for infectious diseases. Furthermore, farmers' and veterinarians' knowledge of antibiotic resistance should be improved and the prudent use of antibiotics encouraged to prevent the development and spread of resistant microorganisms.

Introduction

The transmission of antimicrobial resistant bacteria and/or antimicrobial resistance genes from animals to humans, although not fully investigated (Trauffler *et al*., 2014a, 2014b), exists and can be potentially responsible for therapeutic failures in treating infectious diseases in the human population (van der Fels-Klerx *et al*., 2011). Despite the European Union ban on the use of antibiotics as growth promoters in 2006, their use in therapy and/or prophylaxis /metaphylaxis still remains high in livestock production as reported by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project (EMA, 2016c). Italy is one of the countries where antimicrobial use in veterinary medicine is very high (EMA, 2016c). Although the ESVAC project represents an important international approach for the quantification of antibiotic use in veterinary medicine, different critical points, such as those related to the standardization of units of measurement and data sources, were found (Merle *et al*., 2014; Traufller *et al*., 2014a; EMA, 2016a). Recently, the European Medicine Agency (EMA) has proposed a new approach to quantify antibiotic usage in veterinary medicine, based on the concept of the defined daily dose (DDD), that is analogous to that in human medicine (EMA, 2016a; WHO, 2017). This represents a very innovative approach, overcoming the limits of ESVAC. It takes into consideration the strength of the antimicrobial class, which is fundamental to compare the consumption among antimicrobial classes.

The World Health Organization (WHO) has provided a list of critically important antimicrobials (CIAs) with the highest priority in human medicine. These drugs are characterized by elevated effectiveness; therefore low dosages might be sufficient to treat animals (Merle *et al*., 2014; EMA, 2016c). Third and fourth-generation cephalosporins, fluoroquinolones, macrolides, and, recently, colistin are the antimicrobial classes classified as CIAs by the WHO. Their use in veterinary medicine should be decreased and essentially, they would be prescribed after an antimicrobial susceptibility test has been performed (EMA, 2016a, 2016b, 2016c, 2016d; FAO/OIE/WHO, 2016). The surveillance of antimicrobial use is one of the suggested strategies for the better understanding of antibiotic consumption in livestock. Implementation of strategies for the reduction of their usage would consequently decrease the selection of antibiotic-resistant microorganisms (European Commission, 2015; Speksnijder *et al*., 2015; EMA, 2016a, 2016b; Lhermie *et al*., 2017). Therefore, reliable data on antibiotic consumption by food-producing species and single farms are fervently requested (Trauffler *et al*., 2014a). Antibiotic consumption is high in pig production, compared to other livestock. This is especially true during the first stage of the productive cycle where sows and piglets are often treated, frequently with CIAs, for therapeutic reasons and for prophylaxis and/or metaphylaxis (Merle *et al*., 2014). Risk analysis is an important tool to better understand and assess factors influencing a particular behaviour or necessity of antibiotics in food-producing animals (FAO, 2011; Teale and Moulin, 2012; EMA, 2015). Qualitative risk assessment is always performed at regional, national and international levels in

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the food-production chain (Landers *et al*., 2012), but it is based only on managerial, structural, and health variables. At the farm level, antibiotic risk should be considered as the probability that an irrational antibiotic use in livestock may have consequences on both human and veterinary public health. In this study, an evaluation of the qualitative use of antibiotics in the pig breeding farms of the Umbria region is proposed. It is based on reliable data on the use of antimicrobials and was evaluated with a *DDD-based* method, as suggested by EMA.

Materials and Methods

Data collection and analysis

All the breeding sow farms, with more than 60 reproductive females, were selected in the Umbria region (Central Italy). Data on type of farming and number of reared animals were collected from the national animal database (https://www.vetinfo.sanita.it/). Information about each farm, general characteristics, health status, and management were collected using both a questionnaire given to farmers and an analysis of the registers of treatments. The questionnaire was developed by a working group composed of public veterinarians, scientists, and experts in the veterinary drug and pig industry.

All the antibiotic administrations from 01/01/2016 to 31/12/2016 were evaluated and stored in a database using Microsoft Excel and Microsoft Access. The following information was collected for each antibiotic treatment: commercial name, dosage and duration of therapy with withdrawal periods, productive category, number and age of treated animals, and diagnosis. Data on the antimicrobials [active ingredients (a.i.) their strength, expressed in mg/g or mg/mL; recommended daily dose for each productive category, expressed in mg/kg body weight] were collected from the national veterinary drug handbook (https://www.vetinfo.sanita.it/j6_prontuario/public/)

Active ingredients were classified by their antimicrobial class according to the WHO indications (WHO, 2017). In particular, the analysis was performed taking into consideration all the antibiotics (AB) and CIAs. The monitoring was performed in all the individual farms that were investigated by productive categories and administration routes.

The estimation of AB and CIAs consumption was performed using the *DDD-based* approach, as suggested by the EMA (EMA, 2016a). It was evaluated using the following indicators: prescribed DDDs = total mgs of each a.i./provided EMA DDDvet value of this a.i.; DDDs/1000 animals-*die* = [prescribed DDDs/(number of reared animals X day of observation (365)] X 1000; prevalence (%) = (number of treated animals/number of reared animals) X 100; DDDs/animals = prescribed DDDs/number of treated animals.

Prescribed DDDs and DDDs/1000 animals-*die* were used as the indicators for antibiotic consumption. Prevalence and DDDs/animals, respectively, were indicators of antibiotic exposition and intensity of antibiotic use. In addition, dosage appropriateness was evaluated for each a.i. as the ratio between the dose used and the does suggested by the drug leaflet, as suggested by Merle *et al.* (2014). Standard body weights used for dosage appropriateness were those provided by the EMA in the ESVAC project (EMA, 2016c).

Data collected from the questionnaire and from the antibiotic consumption and dose appropriateness analysis were used to perform the on-farm *qualitative antibiotic use evaluation* (Appendix).

The working group, which has built the questionnaire, provided a score from 0.5 to 3 for each used variable for the evaluation of antibiotic use, following the indications provided by different public authorities and authors (FAO, 2011; Italian Ministry of Health, 2012; Teale and Moulin, 2012; RUMA, 2013; EMA, 2015; FAO/OIE/WHO, 2016; EFSA, 2017). Assigned scores can be seen in Appendix.

For each considered farm, the antibiotic risk profile was evaluated by the sum of all the *each variable assigned scores*. The average score value was calculated and the farms were classified using the following system: farm score ≥ average score + standard deviation (σ): high antibiotic risk; farm score < average score + σ and > average score – σ: medium antibiotic risk; farm score ≤ average score value – σ: low antibiotic risk.

Statistical analysis

Statistical analysis was performed using the software R 3.2.2. Simple logistic regression was used to determine if a high number of bred animals is correlated with a high antibiotic consumption. For this purpose, farms were split into a high and low number of reared animals, based on the average value of reared animals in all the farms investigated. Antibiotic consumption was evaluated as a relationship between DDDs/1000 animals-*die* calculated in each farm and DDDs/1000 animals-*die* evaluated in all the farms. Statistical analyses were performed to determine correlations among the inappropriateness of the dosage, use of CIAs, administration route, and productive categories by evaluating the odds ratios (OR). The analyses were performed on each individual farm and on all the investigated farms collectively. Pearson's chi-squared test was used to determine statistical significance and $P<0.05$ were considered significant.

Results

Eighteen *from-farrow-to-wean/finish swine farms* with > 60 heads of breeding sows were identified in the Umbria region. Only 14 accepted to participate to the study. A total number of 36096 animals were reared in all the monitored farms during 2016. They were composed mostly of suckling piglets (SP) and weaners (W) (64.96%), followed by sows and boars (24.75%) and fattening-finishing pigs (10.29%), bred only in five farms. The arithmetic mean of the reared animals in the 14 farms was 2578.29 (standard deviation [σ] =1850.13) and the 28.57% of the farms housed a higher than average number of animals. There were 2158 antibiotic treatments and 7215.58 x 10^4 prescribed DDDs. As to DDDs/1000 animals-*die,* 35.73% of the farms registered a higher consumption compared with the total amount of DDDs/1000 animals-*die* (Table 1). The analysis of the CIAs highlighted a consumption of 2825.82 x 10^4 prescribed DDDs, corresponding to 2857.16 DDDs/1000 animals-*die.* CIAs prescribed using DDDs were 39.19% of the total prescribed DDDs. Four out of 14 farms (farms 1, 2, 8 and 14) showed a higher consumption of CIAs (29%) (Table 1). An odds ratio of 18 (IC95% 1.51 - 498.33) was found between a high number of bred animals and high antibiotic consumption, although this was not statistically significant (P=0.078).

As reported in Table 1, penicillins, macrolides, tetracyclines, and polymyxins (colistin) were the most common antimicrobials used. Third-generation cephalosporins, penicillins, colistin and fluoroquinolones had the highest prevalence, while sulphonamides and trimethoprim, tetracyclines, and pleuromutilins had the highest intensity of use (DDDs/animals). Analysis of antibiotic consumption per classes and per farms can be seen in Table 1.

The highest percentage of a.i. was related to SP-W, for both AB (58%) and CIAs (78.34%). The *DDD-based* analysis of consumption demonstrated the highest use in sows and boars, while the prevalence was high for SP-W for both total antibiotic consumption and CIAs (Table 2). A statistically significant association was found between the use of CIAs and SP-W (OR = 5.08, IC95%: 4.26-6.07, P<2.2e-16).

Macrolides were the most common antimicrobials in sows and boars, followed by penicillins and tetracyclines. Polymyxins (colistin), penicillins, and tetracyclines were mostly used in SP-W (Table 2). Since it occurred in the majority of the farms (71.43%), gastro-enteric diseases were the main reasons for antibiotic administration, followed by respiratory (28.57%) and reproductive pathologies (14.29%).

Antibiotics were mostly administered orally (84.18% prescribed DDDs) in both SP-W (76.84% prescribed DDDs) and sows and boars (88.07% prescribed DDDs). The oral route was the most used route. This also took into consideration, DDDs/1000 animals-*die* with 5894.28 DDDs/1000 animals-*die* compared to 1107.60 DDDs/1000 animals-*die* used parenterally.

The highest percentage of treatments (47.97%) were classified as *correct dosage*, 34.99% as *under dosage*, and 17.04% as *over dosage* (Figure 1); the *correct dosage* of CIAs administered was 39.67%, while 45.64% were classified as *under-dosage* and 14.69% as *over-dosage*. 54.30% of parenteral treatments and the 33.45% of oral treatments were correctly administered. A statistically significant association was found between oral administration and under- or over-dosages (OR = 2.34, IC95%: 1.98-2.77; *P*<2.2e-16).

SP-W had the highest percentage of incorrect treatments (62.25% AB and 65.53% CIAs), most of which classified as *under dosage* (49.67% AB and 49.83% CIAs) (Figure 1). A significant association (OR = 5.27; IC95%: 4.46-6.24, *P*<2.2e-16) was present between SP-W and *incorrect dosage*.

Statistically significant associations between dosage inappropriateness, use of CIAs and productive categories performed in each farms, evaluated as odds ratios, are listed in Table 3.

The 43% of the farms shows a statistically significant association with the probability of a mistaken antibiotic administration in terms of dosage (dosage inappropriateness) (Table 3 section A). Furthermore, 36% and the 21% of the farms displayed the same significant association for the treatment of SP-W and sows and boars, respectively (Table 3 section A).

Concerning the possible use of CIAs, 14% of the investigated farms exhibited a statistically significant association with the probability of administration of CIAs and 21% showed a significant association for the treatment of both SP-W and sows (Table 3 section B).

Analysis of healthy and managerial

Table 1. Defined daily doses/1000 animal-*die* related to antibiotics treatment per class of drugs as evaluated in each individual farm and in all the investigated farms collectively, with the addition of prevalence and defined daily doses/animals data.

Antimicrobial class	Number of farms 1	2	3	4	5	6	7	8	9	10	11	12	13	14	Consumption evaluated in all the investigated farms: DDDs/1000 animals-*die*	Prevalence (%)	DDDs/ animals
	DDDs/1000 animals-*die*																
Amphenicols	0	258.80	176.83	0	1260	11.19	533.04	171.99	0	174.96	0	0	0	285.96	149.75	71.50	57.39
Aminoglycosides	923.91	378.92	0	561.53	24	44.31	521.38	316.39	0	0	113.84	0	2.69	57.42	240.09	157.02	41.90
Third-gen. cephalosporins*	913.12	259.53	0	0	10	115.79	346.72	571.24	0	93.31	33.03	0	0	48.11	240.12	545.17	12.07
Fourth-gen. cephalosporins*	0	118.45	0	0	0	16.79	0	0	0	0	0	0	0	1038.11	107.93	21.25	139.17
Fluoroquinolones*	142.55	148.28	51.93	69.94	0	33.36	273.72	371.15	152.51	255.23	128.29	7.16	461.08	1496.62	353.14	405.88	23.84
Lincosamides	0	0	0	0	500	0	0	0	0	0	39.70	0	0	475.96	74.39	12.89	158.10
Macrolides*	71.61	159.43		62.74	520	334.62	357.66	4699.07	999.94	34.99	84.31	0	590.73	776.54	1256.74	195.49	176.14
Penicillins	483.86	4991.67	183.20	141.96	1240	376.98	1437.94	1202.34	1020.65	1150.20	308.99	217.35	4057.37	0	1314.79	446.80	80.63
Penicillins (+ beta-lactamase inhibitors)	0	0	0	0	0	0	0	0	0	0	0	0	0	61.63	6.04	1.81	91.54
Pleuromutilins	1067.00	2119.55	0	0	0	920.89	564.38	270.11	0	919.96	26.39	0	205.23	0	388.61	49.80	213.82
Polymyxins (colistin)	1527.32	3114.36	0	209.10	776.52	47.39	1333.74	1005.23	1306.12	222.69	36.41	0	22.81	2356.18	899.23	445.25	55.34
Sulfonamides	0	104.14	0	0	0	0	0	0	0	0	0	0	0	0	4.33	0.29	411.54
Sulfonamides (+ trimethoprim)	0	661.17	0	0	0	0	0	1335.32	0	0	0	0	1564.26	937.59	588.37	34.80	463.20
Tetracyclines	2016.65	4734.32	10636.28	1340.00	0	1152.60	1442.94	338.07	1224.16	1626.24	391.87	0	256.87	1574.57	1081.95	87.65	338.23
Trimethoprim (+ sulfonamides)	0	647.10	0	0	0	0	0	1340.17	0	0	0	0	1570.68	943.23	590.13	34.80	464.59
Total antibiotic consumption	7146.02	14171.68	11048.24	2385.27	4409.57	3053.93	6811.52	11621.08	4703.39	4477.58	1162.84	224.52	8731.72	10051.93	7295.61	-	-
CIAs	2954.60	3043.28	51.93	341.79	1156.25	547.95	2311.84	6646.68	2458.57	606.22	282.04	7.16	1074.62	5715.57	2857.16	-	-

DDDs, defined daily doses; CIAs, critically important antimicrobials. *Critically important antimicrobials.

variables used for the evaluation of antibiotic use is summarized in Appendix. The open-cycle production system (weaners production) was applied to 71% of the farms. Recurrent infections, especially gastroenteritis (71.43%), required antibiotic therapy in 57% of the 14 farms. Among these, in 29% of the holdings, the antibiotics were administered as *therapy* without any diagnosis, while the prophylactic or metaphylactic use of AB was documented in 50% of the farms.

The average score of antibiotic use was 30.96 (σ = 6.99). Three farms were classified at high antibiotic risk (21%), while 9 (65%) and 2 (14%) were medium and low antibiotic risks, respectively.

Discussion

Our study represents the first Italian trial where antimicrobial consumption data were utilized for the evaluation of an *antibiotic risk analysis* and *dosage appropriateness* in pig breeding farms for implementing the new *DDD-based* approach, as suggested by the EMA. Our study was carried out on the effective consumption derived from the farm *Register of Treatments* and a specific questionnaire. This kind of approach made it possible to overcome some of limits caused by the evaluation of sale data, as reported in other national and international plans for antibiotic consumption (van der Fels-Klerx *et al*., 2011; Merle *et al*., 2012). Furthermore, it provides the possibility of a more economic *antibiotic use evaluation* by using data that already exists on the antibiotic use on farms, welfare, biosecurity, and structure/management.

Another advantage of our study was the antimicrobial consumption measurement units utilized. As already stated by EMA (EMA, 2016a), the antibiotic consumption analysis based on DDDs can overcome limits of other measurement units due to its basis on the antimicrobial strength and not on the standard animal weight. In our study, antibiotic consumption was expressed as DDDs/1000 animals-*die*, making it possible to *weigh* the data by the real number of reared animals. Such an approach could represent a suitable method to compare among productive categories of pigs, antibiotic classes, and farms. At the same time, it aims to be one of the elective units of measurement for analysing the relationship between antibiotic resistance and antibiotic usage in veterinary medicine (Collineau *et al*., 2016). Regarding productive categories, our results show a higher consumption of antibiotic in sows and boars, compared to SP-W. This is quite surprising, considering that SP-W were often the most frequently treated animals, as showed by other studies (Merle *et al*., 2014; van Rennings *et al*., 2015). The use of a different unit of measurements in our study, could probably explain the highest antibiotic consumption in sows and boars, however further analysis should be done in the Umbria region and in Italy to assess which productive category is really the most treated in pig reproduction farms.

Dosage appropriateness is another major concern related to antibiotic use and the possible spread of antibiotic resistance (Ungemach *et al*., 2006; Merle *et al*., 2014). The possibility of selecting antibiotic-resistant bacteria after any antibiotic administration is common knowledge, especially in the case of a sub-therapeutic dosage (Barton, 2014). In this study, the use of the dosage inappropriateness ratio, expressed as a ratio between the *used dose* and the *recommended dose* from the leaflet, was another important item contributing to the *antibiotic use evaluation* in pig breeding farms. Since the differences between suggested doses are usually shown by different commercial products (*i.e.* dependent on disease severity or animal age) a ± 25% dose margin of correction range was adopted in order to minimize the bias, depending on the interpretation of the ratio (Timmerman *et al*., 2006). Our data revealed a correlation between inappropriate dosing and oral antibiotic administration, which could represent a risk of the increase in antibiotic resistance in pig production (Burow *et al*,

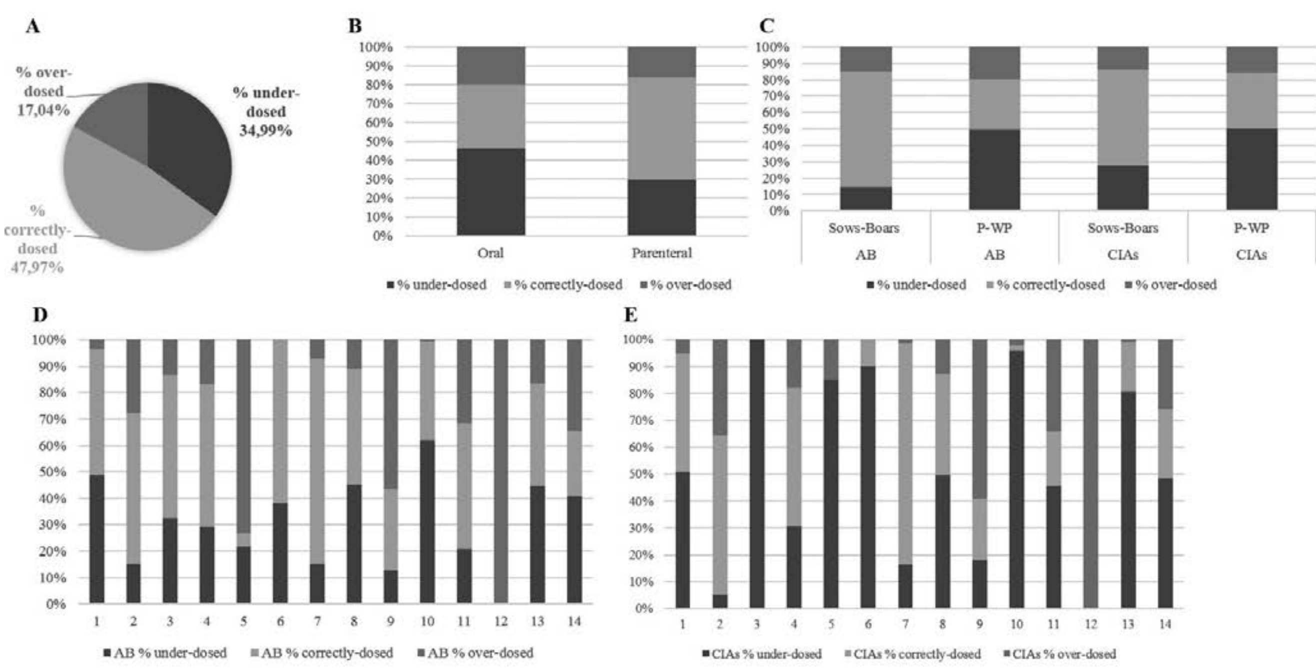

Figure 1. Analysis of appropriate dosing. A) total antimicrobial treatments, B) appropriateness per administration route, C) appropriateness per productive category, D) appropriateness of antibiotics in each individual farm, E) appropriateness of critically important antimicrobials in each individual farm.

2014; Trauffler *et al*., 2014a). High percentages of *under-dosed* treatments administered orally were already reported by other studies (Callens *et al*., 2012; Merle *et al*., 2014). This percentage of inappropriateness can be due to the dosage expression (dose/kg of feed or dose/litre of water) often used for orally administered group treatments of young animals (Timmerman *et al*., 2006). Therefore, it is necessary that clear recommendations with the correct dosage and for improvement of standard procedures for preparation and administration of antimicrobials should be made to both farmers and veterinarians. The tendency to perform oral group treatments in SP-W can partially explain the association between this productive category and inappropriate dosing. The fast growth rate in SP-W makes it difficult to identify an average body weight with which to calculate a suitable antibiotic dosage.

SP-W treatments can be also considered a critical issue in the association between the use of CIAs, especially colistin, and uncorrected dosages, which is responsible for the diffusion of antibiotic resistance (Trauffler *et al*, 2014a). In our work, colistin, which is mainly used in medicated feed, was widely used in SP-W, either as single a.i. or in association with other active agents, as seen by the evaluation of its prevalence. In pig production, it is well-known that colistin is the first-choice antimicrobial for the treatment of gastro-enteric infections, especially by *E. coli,* in SP-W (Timmerman *et al*., 2006; Callens *et al*., 2012; De Bryine *et al*., 2014). A significant reduction of its use in veterinary medicine is recommended because colistin could be one of the last resorts for treating multi-drug resistant infections in humans (EMA, 2016d). In our study, a high consumption of colistin was considered as suitable item for the evaluation of *antibiotic risk* at the farm level.

The most used antimicrobials emerging from our survey were similar to those reported in other countries (Callens *et al*., 2012; Merle *et al*., 2012; De Briyne *et al*., 2014; Merle *et al*., 2014; Trauffler *et al*., 2014, 2014b). The larger amount of prescribed products were broad-spectrum antibiotics, either as single a.i. (*i.e*. ampicillin) or in association with other a.i*, i.e.* amoxicillin plus colistin.

Macrolides were the most administered CIAs class, also showing high prevalence rates and DDDs/animals.

Due to the importance of macrolides for the treatment of campylobacteriosis infections in humans, their use should also be reduced in *from-farrow-to-wean/finish* pig farms in the Umbria region by improving vaccination and good management/hygiene practices.

In addition, it could be advisable to promote the use of other antimicrobial classes, such as pleuromutilins or tetracyclines, which have a similar spectrum of action and are not classified as CIAs by WHO (Timmerman *et al*., 2006).

In the investigated farms, the consumption of other CIAs antimicrobials (third and fourth- generation cephalosporins and fluoroquinolones) was limited. Moreover, they were often administered by the parenteral route, minimizing risk of under- or overdosing, as observed in another study carried out in north Europe (Timmerman *et al*., 2006; Trauffler *et al*., 2014a, 2014b).

Among the investigated farms, the use of antibiotics as prophylaxis/metaphylaxis was found in 29% of the farms and was not supported by antibiotic susceptibility tests. This protocol for antibiotic use must be reduced because such a misuse could increase the risk of antibiotic resistance spreading. At the same time, biosecurity and managerial improvements have to be carried out (Lhermie *et al*., 2017).

In our study, in order to evaluate the use of antibiotics, we also considered other aspects, such as structures, management, biosafety, vaccination programs, that might be useful for reducing antibiotic use in pig production (Laanen *et al*., 2013; Raith *et al*., 2016).

Among the 14 investigated farms, the *all-in-all-out* system was partially applied. Mainly due to the difficulties with its implementation in the *traditionally shaped* and

Table 2. Consumption of antibiotics and critically important antimicrobials in suckling piglets and weaners and sows and boars per classes of drugs.

Antimicrobial class	SP-W				Sows and boars			
	Prescribed DDDs (x10^4)	DDDs/1000 animals-*die*	Prevalence (%)	DDDs/ animals	Prescribed DDDs (x10^4)	DDDs/1000 animals-*die*	Prevalence (%)	DDDs/ animals
Amphenicols	88.81	138.23	107.86	35.12	49.15	200.58	11.85	463.95
Aminoglycosides	209.35	325.85	230.92	38.67	25.25	103.05	27.06	104.35
Third-gen. cephalosporins*	237.07	368.99	839.15	12.05	0.42	1.70	0.11	416.67
Fourth-gen. cephalosporins*	6.05	9.42	19.19	13.45	0	0	0	0
Fluoroquinolones*	128.50	200.01	615.16	8.91	167.82	684.86	24.03	780.90
Lincosamides	100.90	157.05	11.49	374.39	1.92	7.85	0.69	310.17
Macrolides*	117.41	182.75	255.35	19.61	1095.14	4469.27	34.10	3590.63
Penicillins	502.75	782.51	683.52	31.37	863.53	3524.07	119.03	811.25
Penicillins + beta-lactamase inhibitors	5.98	9.30	2.78	91.54	0	0	0	0
Pleuromutilins	95.58	148.77	44.14	92.35	288.77	1178.45	102.30	315.65
Polymyxins (colistin)*	621.47	967.31	664.50	39.89	212.70	868.03	41.43	574.09
Sulfonamides	0	0	0	0	4.08	16.65	1.04	438.71
Sulfonamides (+ trimethoprim)	87.86	136.76	20.68	181.16	463.80	1892.77	75.29	688.85
Tetracyclines	387.53	603.18	82.59	200.12	607.32	2478.46	146.12	464.76
Trimethoprim (+ sulfonamides)	87.77	136.61	20.68	180.96	465.58	1900.01	75.29	691.48
Total antibiotic consumption	2677.02	4166.73	3598.01	31.73	4245.47	17325.74	658.33	721.11
CIAs	1110.50	1728.48	2393.36	47.70	1476.07	6023.86	99.68	4762.70

SP-W, suckling piglets and weaners; DDDs, defined daily doses; CIAs, critically important antimicrobials. *Critically important antimicrobials.

continuous pig-flow system production farms. The lack of the adoption by the *all-in-all-out* system could be partially replaced by suitable standardized procedures for cleaning/disinfection that would rotate the disinfectants in order to minimize the development of disinfectant-resistance (Postma *et al*., 2015).

Generally, the vaccination protocol adopted by each of the 14 farms was to address the improvement of animal health, mainly an improvement in the rates of gastro-enteric infections such as colibacillosis, in sows, suckling piglets and weaners. The appropriate implementation of suitable vaccination plans, combined with proper management, may play an important role in the reduction of antimicrobial use (Postma *et al*., 2015; Raith *et al*., 2016).

The variables used to determine statistically significant associations between the use of CIAs and inappropriate dosing provided a more accurate evaluation of antibiotic use the 14 farms. Farms 1, 6, and 7, followed by the same veterinarian, registered a negative association with inappropriate dosing. This means that the treated animals (in total or by productive categories) frequently received the correct antimicrobial dose. Alternatively, a positive association was seen at farms 8 and 13, both served by the same veterinarian, where the possibility of inadequate dosing was high. Concerning the treatment of breeding stock (sows and boars) with inappropriate doses, a negative association was seen in four out of the fourteen monitored farms. These results may indicate that adult animals are treated more accurately than the young ones, most likely due to a majority of individual and more precise treatments. However, some differences, must be reported farm by farm.

In summary, the results of our analysis on antibiotic risk showed that only 3 farms (21%) out of the 14 are classified as *at high risk*, while the majority were into the two remaining categories (65% *medium risk* and 14% *low risk*). These results suggest that high problematic *from farrow to wean/finish* pig farms in the Umbria region in terms of antimicrobial use are few, even if actions to improve management, biosecurity, diagnostic methods and farmers/veterinarians knowledge should be done to reduce the *high risk* and the *medium risk* farms.

Table 3. Statistically significant associations evaluated in each admitted farm between antibiotic treatments and inappropriate dosing (A) and use of critically important antimicrobials (B) performed on the total reared animals and on each productive category.

Farm	A: Dosage inappropriateness		
	Total reared animals	SP-W	Sows and boars
1	-	-	OR: 0.30; IC95%: 0.09-0.78; P=0.03
2	OR: 0.63; IC95%: 0.51-0.79; P= 4e-15	-	OR: 0.14; IC95%: 0.07-0.25; P=4.99e-12
3	-	OR: 0.25; IC95%: 0.09-0.64; P= 0.005	OR: 2.99; IC95%: 1.17-7.89;P=0.03
4	-	OR: 0.26; IC95%: 0.14.046; P= 2.46e-06	OR: 10.80; IC95%: 2.76-71.11; P=0.0005
5	OR: 17.65; IC95%: 7.30-58.03; P= 6e-14	-	-
6	OR: 0.54; IC95%: 0.38-0.75; P= 0.00037	-	OR: 0.52; IC95%: 0.30-0.87; P=0.02
7	OR: 0.22; IC95%: 0.17-0.29; P< 2.20e-16	OR: 0.08; IC95%: 0.05-0.11; P< 2.20e-16	-
8	OR: 1.24; IC95%: 1.05-1.47; P=0.011	OR: 2.49; IC95%: 1.90-3.30; P=6.22e-11	OR: 0.74; IC95%: 0.55-0.98; P= 0.04
9	OR: 2.06; IC95%: 1.06-4.24; P=0.05	-	-
10	OR: 2.20; IC95%: 1.55-3.18; P=1.37e-05	OR: 13.76; IC95%: 5.13-56.26; P=1.6e-08	-
11	-	OR: 5.53; IC95%: 2.24-18.41; P=0.0004	-
12	-	-	-
13	OR: 1.50; IC95%: 1.15-1.95; P=0.002	OR:8.97; IC95%: 4.26-23.06; P=1.03e-09	-
14	OR: 2.90; IC95%: 2.02-4.25; P=6.90e-9	OR: 2.63; IC95%: 4.26-23.06; P=0.001	OR: 5.20; IC95%: 2.70-10.5; P=3.23e-07
Farm	**B: CIAs use**		
	Total reared animals	**SP-W**	**Sows**
1	OR: 5.08; IC95%: 4.26-6.07; P<2.2e-16	OR: 3.31; IC95%: 2.18-5.21; P<2.34e-08	-
2	-	OR: 0.44; IC95%: 0.33-0.59; P<4.26e-08	OR: 3.34; IC95%: 2.34-4.76; P=9.47e-12
3	OR: 0.45; IC95%: 0.20-0.92; P= 0.05	OR: 0.14; IC95%: 0.03-0.42; P=0.0006	-
4	OR: 2.17; IC95%: 1.32-3.62; P= 0.003	-	OR: 10.95; IC95%: 3.71-39.81; P=2.27e-06
5	OR: 0.48; IC95%: 0.28-0.79; P= 0.006	OR: 0.13; IC95%: 0.03-0.39; P=0.0003	-
6	-	OR: 5.38; IC95%: 2.58-13.10; P=8.26e-06	OR: 0.47; IC95%: 0.24-0.87; P=0.03
7	-	-	OR: 0.54; IC95%: 0.28-0.95; P=0.05
8	OR: 0.83; IC95%: 0.708-0.98; P= 0.03	-	OR: 0.59; IC95%: 0.42-0.82; P=0.002
9	-	-	-
10	-	-	OR: 0.25; IC95%: 0.08-0.63; P=0.08
11	-	-	-
12	-	-	-
13	-	OR: 4.18; IC95%: 2.59-7.11; P=3.78e-09	-
14	-	OR: 0.63; IC95%: 0.41-0.95; P=0.04	OR: 5.04; IC95%: 2.66-9.68; P=1.68e-07

OR, odds ratio; IC, interval of confidence; SP-W, suckling piglets and weaners; CIAs, critically important antimicrobials.

Conclusions

Several factors are involved with the decision to prescribe antibiotics in livestock and many quantitative and qualitative methods have been proposed to quantify *antibiotic risk* within farms (Landers *et al*., 2012). The majority of them are considered incomplete because they do not provide information on direct or indirect risks, which are the basics of risk classification.

Furthermore, these proposed approaches were essentially based on the personal evaluation of farm characteristics and were never applied to large-scale trials (Landers *et al*., 2012). Our study was able to enhance these critical points. It also represents the first approach in Italy where the data related to antibiotic use in pig farms were collected directly from the farm and utilized as a variable outcome in order to classify the *antibiotic risk*.

The use of antibiotics within pig breeding farms (*from farrow to wean/finish*) in the Umbria region should be strictly controlled because it could become a concern for the public health in terms of antibiotic resistance selection and possible presence of residues in pig productions. Therefore, even if the number of *high risk* farms is encouraging, an improvement in management and biosecurity and more responsible antibiotic treatment decisions should reduce the number of farms in the higher risk categories (*high* and *medium* categories). Furthermore, the use of antibiotic susceptibility tests should be encouraged and/or made compulsory to reduce the use of broad-spectrum antimicrobials, especially CIAs, and increase the use of narrow spectrum antibiotics.

The antibiotic treatment of *suckling piglets-weaners*, especially via the oral route, could be considered as an important critical issue and the accurate and strict control of oral administration may be necessary for minimizing the *antibiotic risk*.

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