Risk Factors for Antibiotic Treatment of Pigs Between Birth and Slaughter – A Longitudinal Study

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Abstract

Background: Recently, we found an association between antibiotic treatment and antibiotic resistance in fecal *Escherichia coli* from rearing pigs during their life. In this study, our aim was to investigate potential risk factors for antibiotic treatment at different production stages of these pigs.

Results: In a longitudinal study, antibiotic use was recorded in commercial pig production chains, starting in 29 breeding herds. Information on housing system and management, management of animals and feeding, animal health and performance was surveyed in the herds. In total 55, 57 and 66 variables were evaluated for the production stages suckling, weaning and fattening. In descriptive and univariable analyses seven to eight variables per production stage were associated with antibiotic use. In multivariable analyses, rodent control carried out by a company was associated with an increased risk of antibiotic treatment (odds ratio (OR), 6.86, confidence limits, CL, 1.12 – 41.83, $p = 0.023$) at suckling. At weaning, production type (farrow-to-finish vs. movement of pigs to another farm after suckling or weaning; OR 0.15, CL 0.02 – 0.89, $p = 0.023$) was associated with the risk of antibiotic treatment. During the fattening stage, animals were treated more often when the number of weaned piglets per sow and year increased (additional piglet: OR 2.5, CL 0.6 – 29.6, $p = 0.0172$).

Conclusions: Different risk factors were associated with an increased risk of antibiotic treatment in the individual production stages. Therefore, focus on specific measures, especially at suckling and weaning, when most antibiotics are used, is needed. Further research on key factors driving antibiotic use and the causative pathogens that require treatment is necessary in pig production.

Background

Pig production contributes highly to the global and European meat production (e.g. year 2018; 1). Currently, 88% of European pig production batches get treated with antibiotics at least once (2). The European Union targets for sustainable food production foresee a reduction of antimicrobial sales for farmed animals and aquaculture by 50% to the year 2030 (3). Antibiotic use is associated with antibiotic resistance in pigs (4). In addition, we recently found an association between antibiotic treatment and resistance of commensal bacteria at different production stages during the life of reared pigs (5). Since resistant bacteria reduce treatment options for farm animals and can spread from livestock to humans (6, 7), it is important to identify key factors driving antibiotic use in pig production in order to reduce antibiotic use in pigs.

Several recent studies found a range of risk factors and intervention measures to be linked with antibiotic use and treatment frequency. Enhanced biosecurity can help to reduce antibiotic use and treatment frequency in the pig production in Europe (8–10). Hygienic water supply of suckling piglets and an all-in-all-out-system for weaners were associated with lower antibiotic use (9). Increased weaning age tended to be associated with reduced antibiotic use in farrow-to-finish herds of four European countries (8). Integrated herds had lower antibiotic use compared with herds with only finisher pigs (11). Breeding units

had lower antibiotic use than weaner or fattening herds (12). The effect of herd size was controversial. One study found smaller herds were having more antibiotic use per finisher (11). Another study reported larger herds to use significantly more antibiotics (12). A third study reported, not the herd size as such but the interaction between the veterinarian in charge and herd size were linked with treatment frequency (13). Overall, current knowledge on candidate factors to be addressed at different production stages for reducing antibiotic use is fragmentary. However, it is crucial to identify action points for the reduction of antibiotic use in pig production. This reduction is highly relevant for animal health as well as consumer protection.

Patterns of treatment indications and applied antibiotic groups differ between production stages (5, 9, 13, 14). Weaners were most frequently treated with intestinal and respiratory disorders, sucklers were mainly treated for streptococcus infection, being the primary indications of treatment per production stage (5). A study on Danish pig production found constantly prevalent intestinal diseases and relatively more treatments of respiratory disorders over time as main reasons for treatment (14). The findings indicate reasons for suboptimal conditions of the pigs during their life. For these reasons, key factors to reduce disease incidence, antibiotic use – and thereby antibiotic resistance – may be different between production stages.

Farmers are interested in reducing antibiotic use and resistance but to are at the same time concerned about practicability and proficiency of measures to reduce antibiotic usage (15, 16). Biosecurity practices were found to be a cost-effective way to reduce antibiotic use (17) and economic aspects were evaluated not to be a barrier for improving biosecurity (16). Increased biosecurity levels and decreased antibiotic use were associated with an increased number of weaned piglets, higher weight gain and reduced mortality in finishers (18). The more knowledge farmers had about antibiotic use and resistance, the less antibiotics they used (19). Visschers, et al. (15) and Kramer, et al. (19) concluded on the need to gain knowledge how to teach farmers reducing usage by applying prophylactic measures.

Based on our previous results on the association of antibiotic use and resistance, we wished to identify key factors with a potential to reduce antibiotic use at the different production stages in this longitudinal study. We aimed to investigate putative risk factors for antibiotic use at herd-level in German pig production chains from birth to end of the fattening period. Our hypotheses were that 1) factors affecting antibiotic use at suckling, weaning and fattening can be identified and that 2) these factors differ between production stages.

Results

Farms and animals

In total, 29 breeding farms were recruited for participation in the study. Of these 29 farms, 19 were farrow-to-finish herds. Another nine farms sold the weaners to fattening farms. One breeding farm sold the piglets to a weaning farm, which again sold the weaners to a fattening farm. Therefore, 29 different production chains were observed (13 in Bavaria, 16 in North Rhine-Westphalia). Two production chains

ended in the same fattening herd. Overall, the 29 production chains involved 39 different herds. Seven pigs from each of two focus litters were selected in each breeding farm.

Antibiotic treatment

Antibiotic treatments to the focus litter pigs were recorded in all 29 production chains. Focus pigs were mainly treated at the weaning stage and often the pigs received more than one treatment, i.e. antibiotic agent per production stage (Table 1; more detailed information presented in (5)). In all 29 chains, treatments were applied to all pigs of both focus litters. As an exception from this rule, two sucklers of one breeding herd and one fattening pig received an antibiotic agent individually (via injection) while none of the other pigs of their focus litters were treated. Despite these individual treatments, the litters were classified as “untreated” at the respective production stage. At suckling, all treatments were administered individually (via injection or drench) once or twice. At weaning exclusively oral group administration via water or feed was used for five to ten treatment days. During fattening, injection on one or two days or feed administration for three to 20 days was used. Treated indications and administered agents were described in Burow, et al. (5).

Table 1

Kind and number of antibiotic treatments to focus herds and litters per production stage¹

Production stage	Number of				Applied antibiotic classes
	treated focus herds ²	treatments of focus herds	treated focus litters ³	treatments of focus litters	
Suckling	4	9	8	16	Aminoglycosid, Penicillins
Weaning	15	18	30	36	Penicillins, Tetracyclines, Polymyxins, Macolides, Other
Fattening	4	4	8	8	Tetracycline, Macrolide
¹ in the 29 production stages					
² both focal litters treated					
³ at least half of the piglets per litter treated					

Input variables of housing, management, health and performance

Questionnaire information on housing, management, health and performance was received for all production chains. However, for one of the chains, information from the fattening stage was missing. For other chains, responses to individual questions were missing (Tables 2–4).

Causal diagrams and classification trees

According to the causal diagrams drawn for each production stage, all potential risk factors with $p < 0.2$ in the univariable analysis appeared largely independent with little confounding and were considered in the multivariable analysis.

The classification trees for each production stage, based on variables with $p < 0.05$ in the univariable analysis, was in agreement with the result from the multivariable analysis.

Impact of housing, management, health and performance on antibiotic use

Suckling stage

At the suckling stage, eight variables were associated with antibiotic use at $p < 0.2$ in descriptive tests (Table 2). After univariable analysis, all were considered in the multivariable analysis, except 'Time interval to farrowing when sows enter the nursery' since its p-value was > 0.2 ($p = 0.9992$).

'Cleaning agents used for cleaning the pens' ($p = 0.0298$) and 'Rodent control carried out by a company' (probability, $p = 0.0312$) showed p-values below 0.05 in the univariable analysis. In the multivariable analysis, 'Rodent control carried out by a company' was the only factor that was significantly associated with antibiotic use (odds ratio, OR, 6.86, confidence limits, CL, 1.12–41.83, $p = 0.023$) after backward elimination and forward selection strategy. The value of the Akaike Information Criterion (AIC) was 22.63.

Table 2

Potential risk factors (probability, $p < 0.2$) for antibiotic use at the suckling stage in 29 breeding herds

Variable	Categories	Number of production chains with antibiotic use		P-value in Fishers' Exact test	Categories univariably and multivariably analysed	P-value in type 3 analysis of univariably analysed categories
		No	Yes			
Distance to next livestock farm	1: <1 km	21	2	0.095	1	0.153
	2: 1–3 km	2	2		2	
	3: >3 km	2	0		2	
Cattle housed in the next livestock farm	0: No	8	3	0.139	0	0.103
	1: Yes	17	1		1	
Cleaning agents used for cleaning the pens	0: No	12	0	0.121	0	0.030
	1: Yes	13	4		1	
Rodent control carried out by a company	0: No	20	1	0.079	0	0.031
	1: Inside or outside	3	2		1	
		2	1		1	
	2: Inside and outside	5	0		1	
		1	2		2	
		1	0		2	
		2	0		3	
		4	0		3	
		2	0		3	
		1	2		3	
		4	0		3	
Breed	1: Hybrid DK ¹	5	0	0.013	1	0.051
¹ Danish						
² German						
³ German Landrace						
⁴ German Large Wight						

Variable	Categories	Number of production chains with antibiotic use		P-value in Fishers' Exact test	Categories univariably and multivariably analysed	P-value in type 3 analysis of univariably analysed categories
		No	Yes			
	2: Hybrid DK ² *Pietrain	5	0		1	
	3: Hybrid GE	1	2		2	
	4: Hybrid GE*Pietrain	1	0		2	
	5: DL ³	2	0		3	
	6: DL*Pietrain	4	0		3	
	7: DL*DE ⁴	2	0		3	
	8: DL*D/B E*Pietrain	1	2		3	
	9: Diff. breeds/ crossing	4	0		3	
Time interval to farrowing when sows enter the nursery	1: <1 week	12	0	0.052	1	0.999
	2: 1 week	8	4		2	
	3: >1 week	5	0		3	
Week of life for Porcine circovirus 2 vaccination	0: no indication	4	0	0.167	0	0.053
		11	4		1	
	1: 2.-3. week	10	0		2	
	2: 4.-6. week					
Week of life for <i>Mycoplasma hyopneumoniae</i> vaccination	1: 1 week	14	1	0.156	1	0.095
	2: 2 week	4	0		2	
	3: 3 week	5	3		3	
¹ Danish						
² German						
³ German Landrace						
⁴ German Large Wight						

Weaning stage

At the weaning stage, another eight factors were associated with antibiotic use in descriptive tests ($p < 0.2$; Table 3). All were considered in the subsequent univariable analyses.

Results in the univariable analyses suggested association ($p < 0.2$) of all eight variables, except for 'Week of life for vaccination against *Mycoplasma hyopneumoniae*' ($p = 0.9512$). Beside 'Production type', 'Cleaning pens with warm water' (OR 8.67 CL 0.89–8.67, $p = 0.031$) showed significant association with antibiotic use. 'Number of life births' (OR 0.22, CL 0.05–1.09 $p = 0.055$) and 'Cleaning feeding system after antibiotic administration' (OR 0.15, CL 0.01–1.58, $p = 0.079$) also tended to be associated with a decreased risk of antibiotic use ($p < 0.1$). However, confidence limits of these three variables included the value 1, which contradicts a significant association. In the multivariable analysis (including seven variables in the initial model), 'Production type' was the only significant factor in the final model (OR 0.15, CL 0.02–0.89, $p = 0.023$) after backward elimination or stepwise forward selection.

Table 3

Potential risk factors (probability, $p < 0.2$) for antibiotic use at the weaning stage in 29 production chains

Variable	Categories	Number of production chains with antibiotic use		P-value in Fishers' Exact test
		no	yes	
Production type ¹	1: Farrow-to-finish	12	7	0.014
		1	8	
	2: Piglets/weaners – fattening	1	0	
	3: All stages separated			
Housing places fattening	1: ≤1000	6	7	0.177
	2: >1000	5	1	
Cleaning of pens with warm water	0: no	13	9	0.080
	1: yes	1	6	
Water source	1: Municipal	6	10	0.198 ²
	2: Own well or both	8	5	
Cleaning feeding system after mixing of antibiotics	0: none	12	7	0.142
	1: yes	1	4	
Average weight [kg] at weaning ⁴	Continuous			0.144 ³
Week of life for vaccination against <i>Mycoplasma hyopneumoniae</i>	1: 1. week	7	8	0.101
	2: 2. week	0	4	
	3: 3. week	5	2	
Live births per sow and year	1: <32	5	10	0.128
	2: ≥32	9	4	
¹ Production type analysed in univariable and multivariable analysis as 1: farrow-to-finish vs. 2: movement of pigs to another farm after suckling or weaning (p = 0.05 in Fisher's exact test)				
² Chi-square				
³ GENMOD procedure				
⁴ N = 28, mean 7.1 standard deviation 1.0 kg				

Fattening stage

Antibiotic treatment was applied to four of the 29 production chains at the fattening stage. Seven variables were associated with antibiotic use ($p < 0.2$) at fattening (Table 4) in the descriptive evaluation and included in the further analyses.

In the univariable analyses, 'Hygiene program for water pipe', 'Number of weaned piglets per sow and year' and 'Number of rounds of fatteners per year' were significantly associated with antibiotic use ($p < 0.05$), whereas 'Weight at entrance to growing' and 'Mortality of weaners in the last completed business year' showed tendency of association ($p < 0.1$).

In the multivariable analysis, 'Number of weaned piglets per sow and year' (OR 2.5, CL 0.58–29.58, $p = 0.0172$) was the only significant factor in the final model (lowest value of AIC (10.9) in stepwise forward selection). However, the confidence limits included the value 1, which contradicts a significant association.

Table 4

Potential risk factors (probability, $p < 0.2$) for antibiotic use at the fattening stage in 29 production chains

Variable	Categories	Number of production chains with antibiotic use		P-value in Fishers' Exact test
		No	Yes	
Hygiene program for water pipe	0: no	15	0	0.042
	1: yes	10	4	
Average age [weeks] at entrance to growing ^{1, 2}	Continuous			0.059 ¹
Weight [g] at entrance to growing	1: <30 kg	3	2	0.082
	2: 30 kg	7	1	
	3: >30 kg	10	0	
Mortality of weaners in the last completed business year [%]	1: <1	7	0	0.079
	2: =2	7	0	
	3: >2	4	2	
Number of weaned piglets per sow and year	1: ≤28	11	0	0.137
	2: >28	5	2	
Number of rounds of fatteners per year	1: <3	12	0	0.121
	2: ≥3	13	4	
Live weight of fatteners at slaughter [kg] ³	Continuous			0.142 ¹
¹ GENMOD procedure in SAS				
² N = 22, mean 11.0 standard deviation 1.2 kg				
³ N = 29, mean 119.1 standard deviation 2.9 kg				

Discussion

We identified factors associated with antibiotic use at suckling, weaning and fattening. These factors differed between production stages.

Suckling stage

At the suckling stage, 'Rodent control carried out by a company' was the only significant factor in the multivariable analysis and was associated with higher antibiotic use. In herds with health problems and

increased antibiotic treatment frequency, increased action may be taken by herd managers and veterinarians. This may include ordering of professional pest control. In that case, professional rodent control would rather be a symptom of the problems than the cause of the problems. Literak, et al. (20) observed rodents to be vectors of resistant bacteria and resistance genes of pig intestinal flora. In a Danish study, having a contract with a company for rodent control was associated with turning from livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) negative to positive status (21). Whether LA-MRSA status is directly or indirectly associated with the presence of rodents has not been fully clarified yet but herd size and number of pig suppliers were positively associated with methicillin-resistant *Staphylococcus aureus* occurrence as well (21) and larger herds are more likely to hire a company for rodent control.

‘Cleaning agents used for cleaning the pens’ was associated with a significant higher probability of antibiotic use in the univariable but not in the multivariable analysis. As with the professional rodent control, the use of cleaning agents and increased antibiotic use (and resistance) may be based on high motivation of herd managers to prevent and combat infections (also to humans) especially in large herds and regions of high pig density (21, 22).

A factor addressing production management, ‘Time interval to farrowing when sows enter the nursery’, was identified as potentially relevant in Fisher’s exact test. It seemed that either a very short or long interval would be beneficial. However, this association was not confirmed in the further analyses.

Week of life of vaccinations against Porcine circovirus 2 (PCV2) and *Mycoplasma (M.) hyopneumoniae* showed tendency of association with antibiotic use (increased antibiotic use if vaccination against PCV2 < 1 week, *M. hyopneumoniae* < 3 weeks of life). Generally, vaccines are used in case of an increased number of infections. Vaccination against PCV2 is commonly applied during the 2nd and 3rd week of life, against *M. hyopneumoniae* during first days and the third week of life. These were the periods when also antibiotic treatment was given in some of the observed herds. In a Danish study, vaccination against PCV2 was associated with higher antibiotic use while vaccination against *M. hyopneumoniae* was not (23). In another study, antimicrobial usage from birth until slaughter was positively associated with the number of pathogens vaccinated against (8). Vaccination should be preventive for infections and the need for antibiotic use, but high vaccination schedules may also reflect that increased health issues appeared and high antibiotic use is still needed. Generally, protection given by vaccination is especially important for young pigs being in the transition period between passive and active immunisation. At this early sensitive stage (weaning and suckling), pigs have been described to receive most AMU (5, 13, 14). In contrast to our results, increased internal and external biosecurity showed a decreasing effect on treatment incidence in breeder-finisher and farrow-finish herds and at suckling and weaning stage (8, 24, 25). More generally speaking, a change in herd-specific management can reduce antibiotic use in pig farms (16, 25).

Weaning stage

Weaning was the production stage with the highest antibiotic use in the 29 studied herds (5). At this stage, 'Production type' (farrow-to-finish vs. parts of production chain) was the only significant factor in the final model of the multivariable analysis. Reduced drug use in farms housing the pigs from birth to slaughter was also demonstrated for integrated herds compared to those housing only finishers in Denmark (11). Farms housing only part of the production need to purchase or sell animals, which increases the risk for introduction of pathogens as well as disease spread. Collaboration with several other farms challenges the external biosecurity of a farm. However, a high level of external biosecurity was associated with low antimicrobial use in breeder-finisher herds (24).

The positive association of 'Cleaning pens with warm water' with antibiotic use can be interpreted in line with 'Rodent control by a company', i.e. as a consequence of management action triggered by health problems rather than as a cause of the health problems. Managers are engaged to treat earlier, and take also more action for improving hygiene.

'Cleaning the feeding system after antibiotic administration' was in tendency linked with reduced antibiotic use in the univariable analysis. This could be based on better feasibility of service after infrequent compared to frequent antibiotic use. In herds with infrequent antibiotic use, farmers may be more aware of the risk of resistance selection and therefore avoid using antibiotics. We found less antibiotic use associated with less antibiotic resistance in the respective herds (5). Cleaning the system on the one hand will reduce carry over of antibiotic residues to untreated groups and may also diminish bacterial contamination of water and feeder pipes contributing to a better health status of the animals. This, in turn, will reduce the frequency of events requiring antibiotic treatment.

The in tendency lower antibiotic use in herds with more life births suggests higher production performance linked with better animal health. In line with that, a higher number of weaned piglets, a higher daily weight gain and less mortality were also found to be linked with less antibiotic use in other European countries (18). Pastorelli, et al. (26) found a negative association between high performance measured as high body weight at suckling and weaning and poor sanitary conditions. In conclusion, farmers either have good management in place including adequate biosecurity measures and reach high production performance in an assumably stabilized situation with very limited antibiotic use or they (believe to) need antibiotics to reach or sustain good performance.

Fattening stage

In the multivariable analysis, 'Number of weaned piglets per sow and year' was the only factor being significant for (higher) antibiotic use in fatteners. This factor was also reported to be positively associated with antibiotic use in breeding sows (10). The authors discussed this indicative of a generally more active involvement of the respective farmer and beneficial effects of early treatment. Reduced productivity with a prolonged farrowing cycle was associated with less antimicrobial use and a reduced number of pathogens vaccinated against (8). It has been proposed that more healthy dams may have increased ability to nurse piglets and to transmit antibodies to piglets (8). It needs to be considered

whether genetics of high fertility and short farrowing cycles counteract efforts to reduce antibiotic use and resistance.

In the univariable analysis, 'Number of rounds of fatteners per year' was another measure of production performance that was linked with a higher risk for antibiotic use. Dee, et al. (27) found a higher daily weight gain (and less mortality), i.e. other parameters of production performance, in herds with antibiotic use compared to herds without antibiotic use in finishers. They concluded on the benefit of antibiotic use. Conversely, indicators of lower production performance like higher weaning age and longer farrowing interval were associated with less antibiotic use and thereby turned out to be beneficial management factors in another study (8).

Running a 'Hygiene program for water pipe' was a biosecurity issue associated with more frequent antibiotic use in the univariable analysis. In contrast, others observed lower treatment incidence to be linked with more (strict) biosecurity action with regard to cleaning and disinfection (8, 10). This again raises the question whether increased health impairments and consecutive antibiotic treatments are a consequence of the level of biosecurity or trigger a more active approach of the farmer to biosecurity management.

General discussion

We found only one or few significant risk factors for antibiotic use per production stage in the investigated production chains. These factors address different areas of biosecurity practice in the management of pigs and in their production performance. Identified risk factors differed between production stages, which may highlight different action points between the stages. However, the limited sample size restricted statistical analysis and did not allow to conclude on exclusive lists of influential factors or on general differences. The farms were selected from the regular clients of the animal health services. We cannot exclude sampling bias as farmers with a more active approach and an interest in optimising their herd management could be over-represented. There was an indication that measures had been taken to prevent high antibiotic use. Therefore, we need to be careful with respect to interpretations of cause and effect as exemplified with respect to rodent control. We used documented antibiotic treatments as outcome variable. However, most management and biosecurity factors may first influence health issues and in consequence lead to antibiotic treatments. Therefore, it would be important to consider also the direct influences of the measures on animal health. This is especially important in circumstances with relatively few antibiotic treatments.

Conclusions

Different risk factors were relevant for antibiotic treatment in the individual production stages. Therefore, a focus is needed on specific measures, especially during the suckling and weaning period, when most antibiotics are used. Further research on key factors and pathogens triggering antibiotic use is necessary in pig production.

Methods

Aim

The aim of this study was to investigate putative risk factors for antibiotic treatment at different production stages of rearing pigs.

Farms and animals

This study is part of a comprehensive longitudinal study carried out in German pig herds. Its design has been described previously in more detail (5; doi: 10.1016/j.prevetmed.2019.02.008). In brief:

The target population was pig production herds in Germany that represent the production chain between breeding and fattening, either alone in a farrow-to-finish operation or in combination with other contracted farms. Closed herds (farrow-to-finish) were primarily targeted. However, farms moving pigs to another farm for weaning and/or fattening were also included in the study population. All pigs were housed in closed barns without any access to outside area. Only farms located in the German federal states of Bavaria and North Rhine-Westphalia were included.

Veterinarians of the animal health services in Bavaria and North Rhine-Westphalia selected a convenience sample of breeding farms from their regular client pool. In each recruited breeding herd, two sows were selected prior to farrowing. From the litters of each of the two sows, seven piglets were selected by the veterinarian for detailed follow up.

The study period per individual production chain lasted approximately six months, from birth of the focal litters' piglets to the end of their fattening period. The study period started in April 2015 when the first dams gave birth to focus litters in one breeding herd and ended in October 2016 when the lastborn focus litters in another production chain were sent for slaughter.

Input variables of housing, management, health and performance

In a survey, information on housing system and management, management of animals and feeding, animal health and performance was collected from all involved herds via a questionnaire containing a mixture of closed, semi-closed and open questions. The questionnaire was developed in cooperation with the animal health services in Bavaria and North Rhine-Westphalia. A preliminary version was tested and modified with the help of two voluntary farms. A copy of the final German questionnaire is accessible via the corresponding author. In total 55, 57 and 66 variables were evaluated for the production stages suckling, weaning and fattening. Two veterinarians and one agronomist discussed until agreement about putative causal association and inclusion of each variable in the evaluation of antibiotic use per production stage.

Outcome variable

The evaluated outcome variable was antibiotic use. All antibiotic treatments of the focus litters' pigs from their birth until their slaughter or death were documented. The treatment information included identity, age and number of treated animals, the antibiotic agent, indication for treatment, administration route, date and duration of treatment. The treatment information of focus litters' pigs was recorded on a card following these animals from birth to the end of fattening. Focus litter pigs of one production chain were considered treated at suckling, weaning or fattening if at least half of them received at least one antibiotic agent for at least one day during the respective production stage. Else they were classified as being untreated. Administration of an antibiotic product (one agent or simultaneous application of a combination of agents as e.g. trimethoprim and sulfonamides) for one or more prescribed days was counted as one treatment. In case of recorded group treatment of a litter or herd (and no detailed information for the focus pigs), it was assumed that all living animals of the group, including the respective focus pigs, received the treatment. Since both litters per farm were treated equally in all cases, antibiotic treatment was evaluated on the level of the production chain not on the individual litter.

According to the observational study design, no additional instructions were given to the herd managers regarding antibiotic use before, during or after the study period.

Statistical analysis

Risk factors for antibiotic use (outcome, binary yes/no) in German pig production chains were evaluated. Separate analyses were carried out to model the probability of antibiotic use of an individual production chain (sometimes called 'herd' for simplification) at suckling, weaning and fattening using logistic regression in SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, United States) with the procedure GENMOD in logit transformation. Continuous variables were either included as such in the analyses, or they were categorised if the distribution encouraged an ordinal scale or dichotomisation. Classes of categorical variables were aggregated in order to sum up classes with few cases and to balance frequencies.

Causal diagrams for each production stage were drawn and discussed between two persons to clarify relevance of potential main factors and putative associations between factors and with the outcome variable antibiotic use. It was decided to include all factors in the further analyses.

The association between the individual risk factors and antibiotic treatment was screened per production stage using cross tabulation for categorical variables with chi-square test if at least five cases in the least frequent outcome were given, else with Fisher's Exact test. Continuous variables were tested with logistic regression (GENMOD procedure). In the univariable analysis, all variables were tested with logistic regression (GENMOD procedure). All variables that showed an association with the outcome variable at $p < 0.2$ were considered in the initial model in the multivariable analyses.

Potential risk factors and their association with antibiotic use were further evaluated and visualized using classification trees in R (Version 3.5.3; R Core Team 2019. R: A language and environment for statistical

computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>., package partykit, model ctree).

Finally, multivariable analyses were carried out, using general linear models (in SAS 9.4, applying GENMOD procedure). The model was built based on univariable results ($p \leq 0.2$). If co-linearity was suspected, two multivariable models, including the one or the other variable, were run and results compared. Model reduction was preferably carried out by using backward elimination. In case the full model did not converge, forward or stepwise selection was applied. Decision criterion for elimination or selection was the p-value of fixed effects ($p < 0.05$ as the threshold). The final model included only variables with a fixed effect of $p < 0.05$. In case no variable had a p-value below 0.05, those with a value below 0.1, else those below 0.2 were considered. The fit of the model was evaluated by the AIC (smaller is better). The resulting model was to be checked for confounding (20% change in the estimates when including the potential confounder), to be expanded by all combinations of possible two-way interactions (large model) and to be reduced by stepwise backward elimination ($p < 0.05$ as the threshold). The final model was the one with fixed factors of $p < 0.05$ in tests of fixed effects and the smallest AIC among the models derived from the large model.

Abbreviations

AIC

Akaike Information Criterion

CL

confidence limits

DE

German Large White

DK

Danish Hybrid

DL

German Landrace

GE

German

LA-MRSA

Livestock-associated methicillin-resistant *Staphylococcus aureus*

M.

Mycoplasma

OR

Odds ratio

PCV2

Porcine circovirus 2

P

Probability

Declarations

Ethics approval and consent to participate

Participating farmers were informed about the content of the study and asked for their willingness to participate. Anonymity of data collection was guaranteed.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The group of authors includes one treating and two consulting veterinarians. Their documentation of antibiotic treatments on the participating farms was used for the study. No further interests to declare.

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Authors' contributions

EB: Study coordinator, data analysis and interpretation, major contributor in writing the manuscript. CS: Survey design and data editing. AR and JH: Survey, data collection and interpretation. BAT and AK: Supervision of the study, revision of the manuscript. All authors designed the study, and reviewed, edited and approved the final manuscript.

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