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Factors associated with usage of antimicrobials in commercial mink (*Neovison vison*) production in Denmark

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ABSTRACT

The American mink (*Neovison vison*) is used for commercial fur production in Denmark. In recent years, antimicrobial prescription for Danish mink has been increasing. In this study, the patterns and trends in antimicrobial use in mink were described and a multi-variable variance analysis was carried out with the objective of identifying risk factors for antimicrobial use on herd level. The study was based on register data for 2007–2012. Information on antimicrobial use was obtained from the national database Vet-Stat, monitoring all medicinal products used for animals on prescription level. Data on microbiological feed quality was obtained from the Voluntary Feed Control under the Mink producers Organization, and data on herd size and the relation between farm and feed producer was obtained from the registers at Kopenhagen Fur, based on yearly reporting from the mink producers. Descriptive analysis showed a clear significant effect of season on antimicrobial use, with a peak in "treatment proportions", TP (defined daily doses per kg biomass-days) in May, around the time of whelping, and a high level in the following months. In autumn, a minor peak in antimicrobial use occurred throughout the study period. From 2007 to 2011, a 102% increase in annual antimicrobial TP was noted; on herd level, the increase was associated with an increasing frequency of prescription, and a decrease in the amounts prescribed in months with prescription. A binomial model showed that on herd level, the annual number of months with antimicrobial prescription was significantly ($p < 0.01$) affected by *feed producer, veterinarian, disease* (specific laboratory diagnosis) infection, *herd size* and *year*, with an interaction between *feed producer* and *year*. A log-normal model showed that in months with antimicrobial use, the TP on herd level was significantly ($p < 0.001$) affected by *year, month* (season)*, feed producer*, feed quality *score, veterinarian, herd size* and laboratory confirmed diagnosis of specific infections; additionally the interaction terms *year × feed producer* and *herd size × month* were significant ($p < 0.001$).

In conclusion, antimicrobial use on herd level was significantly associated with the microbiological food quality, the feed producer, and the veterinarian. The prescription patterns varied significantly between veterinarians, and some veterinarians were associated with both larger and more frequent prescriptions of antimicrobials at herd level. Herd size is associated with different prescription patterns. Finally, infection with *Pseudomonas aeruginosa*, astrovirus, influenza virus and *Salmonella* spp. was associated with an increase in antimicrobial use.

1. Introduction

The American Mink (*Neovison vison*) is farmed for its fur in a few countries and the pelt is traded on a global market as dried skin. In the northern hemisphere, the minks are mated in March; mink kits are born around the 1st of May, weaned at 8 weeks of age, and pelted in November. In Denmark, 1465 commercial mink farms were registered in 2014, housing 3.3 million breeding females (Clausen, 2014). The average weaned litter size is around 5.5 mink kit per breeding female under Danish conditions. In the winter period, only the breeding stock will be housed on the farm and breeding males will normally be pelted after mating. In total, 13 feed producers supply the farms with fresh mink feed on a daily basis (from mid-April to the beginning of December) or every second day. Generally, the farms are supplied from the same feed producers throughout

the year(s), resulting in a strictly hierarchical structure, with feed of same composition and quality within groups of farms supplied from a specific producer.

Medicine used for animals in Denmark must be prescribed by a veterinarian, with mandatory recording of the prescription in Danish Veterinary Medicine Statistics, VetStat (Anon., 2011a, 2014). In 2011, a new legislation was implemented obliging all commercial mink farms to sign a contract with a veterinarian; the aim was to ensure animal health and supervision of animal welfare through four mandatory veterinary consultations on the farm annually, with discussion of special relevant topics for the season and documentation in a written report (Anon., 2011b).

Use of medicines including antimicrobials is of pronounced importance for ensuring the physical welfare of the animals in the livestock productions, in curing infectious diseases. However, the total amount of antimicrobials prescribed for use in the Danish mink production has been steadily increasing for almost a decade up to 2012 (Chriél et al., 2012), for no obvious reason. Many factors may affect the use of medicines; the economic break-even between price for the medicine, the value of animal of concern and convenience of administration will affect the decision whether to initiate treatment (Chriél and Dietz, 2003). In the mink production, the new generation of feed trucks with automated dosing equipment for medication has eased the utilization of antimicrobials for oral use.

Antimicrobials are often used for treating unspecific diarrhea or pneumonia, and to a lesser extent in the less frequent outbreaks of contagious diseases such as *Pseudomonas aeruginosa* (*P. aeruginosa*) pneumonia, or for secondary infections after outbreak for mink influenza or canine distemper. Low feed quality or impaired farm management may indirectly lead to increased antimicrobial use. An earlier study of gastrointestinal disorders in mink found that differences between the feed producers as a risk factor accounted for 80% of the variation in occurrence of gastrointestinal disorders (Rattenborg et al., 1999). However, resistance in the bacterial population is amplified by selection pressure from antimicrobial use, which may result in reduced or—in worst case—no effect of the antimicrobial treatment (O'Brien, 2002; Diarra and Malouin, 2014).

The aim of this study was to identify risk factors associated with usage of antimicrobials in the Danish mink production.

2. Material and methods

2.1. Population under study, data inclusion and study design

In Denmark, a farm is defined by an identity code (CHR-ID) within the Central Husbandry Registers (CHR). The CHR-ID was used to merge data from different sources. The study was cross-sectional for the period 2007–2012, including all mink farms complying with the inclusion criteria:

(1) Only farms that were active throughout the study period were included, as indicated by annual reporting of the breeding stock (females) to Kopenhagen Fur. Consequently, farms that were not members of the Danish Fur Breeders Association or had not complied with the annual reporting were excluded. Based on this criterion 6.0% of the antimicrobials prescribed for mink during the study period were omitted.
(2) The 13 feed producers, which were active throughout the study period, were included. All farms associated with one of these 13 feed producers according to the records at Kopenhagen Fur were included. These farms accounted for 93.6% of the antimicrobial usage in mink during the study period, i.e., an additional 0.4% of the antimicrobial prescription for mink was excluded.
(3) One farm with only 20 breeding animals registered in a single year was excluded because either the number of animals was erroneous (~2000 animals registered other years) or the farm did not comply with criterion 1. Accordingly, 0.4% of the antimicrobials prescribed for mink were excluded.

2.2. Data sources, data cleaning and estimation procedures

2.2.1. Animal population and estimation of farm animal biomass

The data on the relation between feed producer and CHR-ID, and the herd size was obtained from the registers at Kopenhagen Fur (Clausen, 2013), based on yearly reporting from all members of the Danish Fur Association.

As the animal biomass fluctuates significantly over the year, the biomass per farm was estimated on a monthly basis. The average weight of a dam and the progeny for a given month was estimated from growth curves (Anon., 2013a), time of birth and pelting, and actual weight data from a sample of farms (Personal Communication, Michael Sønderup,[1] 2013). For each calendar month, the average biomass on a farm related to each dam was estimated as

$$w_{jk} = d_{jk} + n_k \times p_{jk} + a \times m_{jk}$$

where d is the average weight of a dam in month j and year k; n is the size of an average litter for a given year, and p is the average weight of a kit in month j and year k; m is the average weight of adult males in month j, and year k; a is the proportion of breeding males per dam. Almost all males kept for breeding in March are pelted immediately after end of the mating season. After pelting of the production mink (litters) in November, the number of breeding males were assumed to be 1 male per 5 dams during the period December through April; the corresponding number for May to November was only 1 male per 50 dams.

The total live biomass on a given farm was estimated as

$$Biomass_{ijk} = n_{ijk} \times w_{jk}$$

where n_{ik} is the recorded number of dams on a given farm (i) in a given month (j) and year (k).

2.2.2. Vaccine and antimicrobial prescription

Data on all prescriptions of antibacterial medicines and vaccines for mink within the study period (2007–2012) were extracted from the Danish Veterinary Medicine Statistics, VetStat (Stege et al., 2003). The VetStat database has national coverage and contains detailed information about all veterinary prescription of therapeutic drugs and antimicrobial feed additives on species and herd level. Each prescription is represented by a record, including information on date of purchase, product identity and quantity, farm CHR-ID, target animal species, target age group, target disease category, and the identity of the prescribing veterinarian. VetStat data are considered to cover more than 99% of the total prescribed amounts of antimicrobials for veterinary use (DANMAP 2001). In the first step, all records on sales of antimicrobials for local gastrointestinal (GI) or systemic treatment were extracted, when either (1) prescribed for mink (2) and/or prescribed to mink farms with no other animal species recorded in the CHR. When the recipient farm housed mink but animal species was not recorded (ad 2), the records were included only if it concerned medicinal products known to be used in mink. Medicines for topical application were not included in the analyses.

The initial data set comprised 21,972 pharmacy records and 5801 records from the veterinarians. The amounts of prescribed medicine reported by the veterinarian were occasionally clearly erroneous; the structure of these errors indicated that it was most

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likely due to systematic errors in the veterinarians recording system, causing multiplication or division of the reported amounts by package size. Obvious errors were corrected, affecting 22 records on parenteral usage only.

Antimicrobial usage was summarized by the CHR-ID, year and month.

Regarding the vaccines, more than 90% were sold directly from the pharmacy to the farm on veterinary prescription, whereas about 5% was distributed from the pharmacies via the veterinarian. Only information on the number of prescriptions of vaccines (not the actual number of dosages) for each veterinarian and related farm was used in this study for the identification of the main veterinarian on a farm (see Section 2.4.1).

2.2.3. Disease diagnosis

The national reference laboratory for fur animal diseases is part of the National Veterinary Institute (NVI), Technical University of Denmark. The carcasses and/or diagnostic material submitted from the veterinary practices are subjected to a standard necropsy protocol with subsequent relevant routine diagnostic tests. From the laboratory database at the NVI, data on CHR-ID and date of sample submission was obtained for confirmed laboratory diagnoses of astrovirus (enteritis), aleutian disease virus (ADV, a parvovirus), influenza virus, mink enteritis virus (MEV, a parvovirus), canine distemper virus (CDV, a paramyxovirus), *P. aeruginosa* (pneumonia), and *Salmonella* spp. Data on laboratory diagnosis were summarized on CHR-ID and month. It should be noted that the positive diagnoses included in this study do not include cases diagnosed in other laboratories, nor undiagnosed cases.

2.2.4. Feed quality

Mink are fed with a daily produced moist feed, delivered directly to the farms daily in the summer period, and every second day during the rest of the year. Each farm receives feed from only one feed producer. For each feed producer, a voluntary feed control is carried out through test of the ready-to-eat feed (from 12 to 29 samples from each feed producer in 2012) on a regular basis—in most instances on a monthly basis (Christensen et al., 2013). For each sample, at least four analyses of nutrients and ten different analyses reflecting the microbiological quality are carried out. A feed quality score is calculated based on the measures total bacterial count and count of sulfide producing bacteria, fecal streptococci (enterococci) and mold—the higher score, the lower feed quality (Anon., 2015a,b). Low quality or contaminated feed may cause disease outbreaks in the recipient mink farms. Therefore, it was decided to use the highest feed score per feed producer within a given month, as the measure for feed quality, *Score*. The score on a yearly basis (*Score$_{yr}$*) was calculated as a simple mean of the monthly *Score*.

2.3. Measure of antimicrobial use: treatment proportion

The Defined Animal Daily Dose (DADD) was applied in this study as a measure of antimicrobial use, because it is suitable for following trends in antimicrobial use quantitatively over time and across different antimicrobial classes (Jensen et al., 2004; Chauvin et al., 2008; Bondt et al., 2013). The DADD is defined as the mid-range approved maintenance dose for the main indication in the species at hand, for treatment of one kg animal. The DADD is a standardized measure of amounts of antimicrobials, enabling addition of amounts of different antimicrobial agents with varying potency, also taking into account the administration route. As the applied dose may vary, the number of DADDs may be used as a proxy—but not a precise measure—of the amounts of animal biomass that may have been treated.

In this study, the DADD was defined on the level of antimicrobial agent, animal species, and administration route based on the

principles described in DANMAP 2012 (Anon., 2013b). The DADD designates the daily dose required to treat one kilogram body-weight where nothing else is stated. However, no antimicrobial medicinal products are approved for use in mink in Denmark, i.e., no approved dosages are available. As a consequence, the DADDs for oral administration were defined for this study based on recommended doses by Willadsen (2009). For the parenteral drugs, the dosages approved for dogs were applied; when this was not available, the general, non-species specific approved dosage was applied. The DADDs defined for this study are available in online Supplemental Table A.

In order to follow trends in antimicrobial treatment intensity in a given (sub-) population and for comparison between (sub-) populations, the live animal population biomass can be applied as the denominator. In this study, the estimated monthly treatment proportion was calculated as

$$\text{Treatment proportion, TP}_{ijk} = \frac{\text{ND}_{ijk}}{\left(\text{biomass}_{ijk} \times \text{days}_j\right)}$$

where ND_{ijk} is the number of antimicrobial daily doses, DADD, prescribed for farm (i) in a given month (j) and year (k). The number of days in a given month (days_j) was multiplied by the biomass estimated on farm level as described in Section 2.2.1. The TP may also be calculated across a group of farms, e.g., at the national level, in which case the total ND for the group of farms included, divided by the total biomass-days across farms were applied.

2.4. Statistical methods

Data were organized, validated, and analyzed using the software SAS®, version EG 6.1 and version 9.4. Descriptive statistics were performed on the national level, describing differences between feed producers, annual trends and target disease categories. For the descriptive analysis, the TP was calculated for each group of farms within the relevant category (disease category, national level or within feed producer). Further, the trend in the proportion of farms receiving treatment was investigated.

2.4.1. Description of variables

For the statistical modeling, the monthly TP was calculated on farm level. The responsible veterinarian for a given farm in a given year (=a *farm-year*) was identified based on the number of prescriptions of antimicrobials or vaccines to mink farms. Some farms had more than one veterinarian visiting during a year, but usually one veterinarian was responsible for the vast majority of prescriptions, while other veterinarians were visiting (prescribing) only sporadically. The veterinarian with the highest number of prescriptions for a farm in a given year was designated as the "*responsible veterinarian*" on the farm for that year; a dummy variable was assigned in case of farms without veterinarian prescription in a given year. Since the total number of veterinarians visiting Danish mink farms through the period 2007–2012 was high ($n = 444$), the veterinarians were grouped, forming a new explanatory variable '*Vet-group*' assigned to each farm-year. The purpose of grouping was to reduce the number of parameters for the effect of veterinarian to obtain meaningful results and to enable the model to run.

Although disease problems may continue into a consecutive month, it was assumed that the antimicrobial was prescribed in the same month as the diagnosis was established.

The potential explanatory variables were defined as follows:

Class variables:

- '*Feed producer*'—a proxy for feed quality on feed producers level across the study period.
- '*Month*'—a proxy for seasonal effects.

- 'Year'—the calendar year.
- '*Herd size*'—a categorical variable based on the number of dams (breeding stock) registered: small herds (<1500 dams), medium herds (1500–2499 dams), large herds (≥2500 dams).
- '*Disease*'—a categorical variable in a given month for NVI diagnosed astrovirus, ADV, influenza virus, MEV, CDV, *P. aeruginosa*, and *Salmonella* spp.
- 'Disease-count'—the number of positive laboratory confirmed diagnoses on herd level across the year.
- Administration route—(1) only parenteral prescription (2) oral, or oral and parenteral prescription within a given month. (as oral prescription in general greatly exceeds parenteral prescription).
- '*Vet-group*'—a categorical variable representing a single veterinarian (the 20 veterinarians each "responsible" for >67 farm-years) or a group of veterinarian. The groups consisted of veterinarians that were identified as the *responsible veterinarian* in few farms (by year):'*regular prescribers*' were "responsible" in 10–67 farm-years; *occasional prescribers*' were "responsible" in less than 10 farm years. A dummy variable ('*no prescribers*') was assigned for *Vet-group* for farm-years where no *responsible veterinarian* could be identified. The 20 single veterinarians that were the "*responsible veterinarians* in the most farm-years were each included individually. Consequently, the categorical variable '*Vet-group*' included 23 classes. Further details are available in Table 1.

Continuous variables:

- '*Score*'—a proxy for feed quality in a given month (for each feed producer), as defined in Section 2.2.4. The log(TP) was plotted against the variable *Score* to investigate if *Score* could be included in the model as a linear continuously variable. The plot did not show violation of the assumption of linearity.
- $Score_{yr}$—a proxy for feed quality on an annual basis for the feed producer, calculated as the annual average of *Score*. The frequency of months with prescription (Model A) was plotted against the variable $Score_{yr}$ to check the assumption of linearity. A box-plot showed no violation of such assumption.

Random variables:

CHR ID was included as a random effect (CHR-ID) to adjust for between-farm variations. This is the most efficient way of describing the (known) effects of farm, assuming that this factor is of no interest in itself (Dohoo et al., 2009). For both models, CHR ID was modeled as a random effect in the Proc Genmod procedure by applying the farms as a repeated measurement and with an independent structure in the variance matrix. This seemed reasonable since the unstructured matrix showed little correlations. The GEE (Generalized Estimating Equations) method was used for fitting models.

2.4.2. Modeling procedures

Two generalized linear models were developed using the GENMOD procedure in SAS® version 9.4. It seemed reasonable to carry out the analyses using two different models since the majority of the response variable (TP) had months with zero registered prescriptions. Setting the zero TP's to a very small figure and then log-transform all data did not solve the problem with a highly skewed distribution where the majority of the data had the same value with no variance. Consequently two models were developed:

Model A, where the response variable was reduced to a binary outcome (prescription/no-prescription) on monthly level. The data was fitted to a binomial distribution, describing the number of month with prescription out of 12 trials (months) per farm per year (farm-year). The data set comprised a total of 7896 farm-years, each

with 12 trials, and all explanatory variables were defined on farm-year level. The explanatory variables included in the analysis were: *Feed producer*, $Score_{yr}$, *disease count*, *year*, *herd size*, and *vet-group*. The significant level for this model was $\alpha = 0.05$. Even though the data set was very large the transformation into binary data meant loss of information; consequently, there was no need for reducing the significance level for this model in order to avoid significance of very small differences.

Model B, where all zero responses (TP's) were omitted and the positive TP's were log-transformed to meet the assumption of normal distribution. Thus all (81,272) observations with TP = zero were omitted resulting in a data set with 13,480 observations. The explanatory variables included in the log-normal analysis were: *Feed producer*, *score*, *disease*, *year*, *month*, *herd size*, and *vet-group*. CHR-ID was included as random effect. Due to the large size of the data set a significance level of $\alpha = 0.001$ was applied in order to avoid significance of even the smallest differences.

A backwards elimination procedure was applied in order to find the final models only consisting of significant variables. Sidaks multiple comparison test (Šidák, 1967) was applied to investigate which group(s), e.g., of *feed producer*s or *vet-groups* had a significantly different effect from other groups.

2.4.3. Comparison of grading of veterinarians and feed producers in the two models

A comparison between the frequency and the amount of antimicrobial in months with prescription associated with each feed producer was carried out by ranking the feed producers according to the two measurements. The lower the number, the lower was the frequency or amount of antimicrobial prescription. A similar comparison between frequency and amount of antimicrobial within a month associated with each veterinarian was carried out.

3. Results

3.1. Descriptive analysis

The database at Kopenhagen Fur comprised 1799 farms that were active at some point within the study period. Of these farms, 1320 were active throughout the study period, and the final dataset comprised 1316 farms. The initial crude dataset on antimicrobial use comprised 27,773 records amounting to 1564 million DADD. After applying the inclusion criteria, the recorded prescription in the final dataset amounted to 1369 million DADD, corresponding to 87.5% of the antimicrobial prescribed for mink during the study period.

Results of the descriptive analyses of the predictor variables are shown in Table 1, Figs. 1 and 2. The descriptive analysis of antimicrobial use in mink on the national level showed a clear seasonal variation in antimicrobial use: The crude antimicrobial use peaked in May and in autumn, with a high level in between compared with the winter months (Fig. 1). The antimicrobial TP peaked in June–July. The peak in May–July was very prominent, when the mink kits were weaning and the biomass was still low (Fig. 1). In contrast, the autumn peak is small when measured as the treatment proportion, because kits are almost grown at this time. Compared with 2007, the annual treatment proportion had more than doubled (102% increase) by 2011. The proportion of farms receiving at least one prescription per year increased during 2007–2012. Thus, 50% of all mink farms received antimicrobial in 2007, as compared with 82% in 2012. The increase was especially high for the small farms (Fig. 2).

A steady increasing trend in annual antimicrobial use per live biomass was observed through the study period, with a maximum in 2011 (Fig. 1). From 2007 to 2012, oral prescription increased

Table 1
Descriptive statistics of variables potentially associated with antimicrobial use in 1316 farms in Denmark, 2007–2012.

Variable	Scale	Number	Median	Range	SD
Calender year	Ordinal	6 levels		2007–2012	
Calender month[a]	Ordinal	12 levels		01–12	
Feed producer	Categorical	#Farm-years			
a		264	–	–	–
b		498	–	–	–
c		1164	–	–	–
d		366	–	–	–
e		258	–	–	–
f		300	–	–	–
g		54	–	–	–
h		1476	–	–	–
i		1266	–	–	–
j		432	–	–	–
k		1296	–	–	–
l		204	–	–	–
m		318	–	–	–
Feed quality	Continuous				
Score[a]			6.2	0.1–22.1	3.1
Score$_{yr}$[b]			6.2	2.7–13	2
Herd size	Categorical	#Farms			
<1500 dams		581	914	100–1499	340
1500–2499 dams		399	1900	1500–2499	286
≥2500 dams		336	3843	2500–11,300	1463
Disease[a,c]	Categorical	#Confirmed diagnoses			
Enteritis, Astrovirus		32		–	
Enteritis, Parvovirus		13		–	
Plasmacytosis		96		–	
Distemper		66		–	
Ps.aeruginosa		98		–	
Salmonella spp.		21		–	
Influenzavirus		27		–	
Disease count[c,d]	Ordinal		0.02	0–2	0.15
Vet-group[e]	Categorical	#Veterinarians	#Farm-years per veterinarian		
		(% of farm-years)	Mean	Range	SD
Frequent prescriber	20 categories	20 (40%)	232	120–524	115
Regular prescriber	Cat. = 17	93 (29%)	24	10–67	15.4
Occational prescriber	Cat. = 19	339 (12%)	2.9	0–9	2.2
No prescriber	Cat. = 23	no vets (19%)			
Treatment proportion[f]	Continuous		0.04	0–8.5	0.18

[a] Tested only in the log-normal model.
[b] Tested only in the binomial model.
[c] Laboratory confirmed diagnosis.
[d] Number of laboratory confirmed diagnoses per year.
[e] Group of veterinarians defined based on the number of farms for which they are the responsible (most frequent prescribing) veterinarian: 'Frequent prescribers'—the top-20 veterinarians, each responsible for more than 67 farm-years. 'Regular prescribers'—group of 93 veterinarians, each the responsible vet in 10–67 farm-years. 'Occasional prescribers'—group of 339 veterinarians, each the responsible vet in less than 10 farm-years.
[f] Outcome variable in the log-normal model: antimicrobial use measured as the treatment proportion = defined daily doses per biomass × days.

from 23 to 45 DADD/1000 biomass days (by 95%) and parenteral prescription increased from 0.45 to 0.87 DADD/1000 biomass-days (86%). In absolute numbers, the increase in oral prescription amounted to 98% of the total increase. The largest absolute increase was noted from 2008 to 2009 (from 21 to 25 DADD/1000 kg biomass) and from 2010 to 2011 (from 36 to 45 DADD/1000 kg biomass), due to large increases in oral use. For parenteral use, the largest increase was noted from 2007 to 2008 (from 0.45 to 0.64 DADD/1000 biomass-days) and from 2009 to 2010 (0.60 to 0.74 DADD/1000 biomass-days). From 2009 to 2011, prescription for oral use increased by 27% from 36 to 46 DADD/1000 biomass-days, or 45 times more than the absolute increase in parenteral use in the same period.

Data for the binomial model showed that number of months with only parenteral use increased by 250% from 2007 to 2012 (230 to 857), mainly from 2009 to 2010 (from 270 to 497) and from 2010 to 2011 (from 497 to 847). The number of months with prescription for oral use doubled during 2007 to 2012 (from 1118 to 2298), due to a more steady increase.

3.2. Multi-variable variance analysis

3.2.1. The Binomial model (Model A)

This dataset contained 7,896 observations (=farm-years), each with 12 trials (12 months), comprising in total 13,480 events (farm-months with prescription) and 81,272 non-events (farm-months without prescription).

The final model included *year* ($p = 0.004$) and the highly significant variables ($p < 0.0001$) *feed producer*, *vet-group*, *herd size*, *count* of confirmed disease outbreaks, and the interaction term *feed producer × year*. *Year* was included as a categorical variable to allow for detection of non-linear associations. *Year* was significant meaning that the increased use of antimicrobial over the years could not entirely be explained by the other factors in the model. 2007 and 2008 were significantly lower than 2009 and 2010, which again were significantly lower than 2011 and 2012. The significant main variables in the binomial model are shown in Table 2, and the effects of the individual *feed producer* and *vet-group* are shown in Fig. 3. The confidence interval for some *feed producer*s was very large due to a considerable lower number of samples. The interaction term *feed producer × year* showed significantly different development over
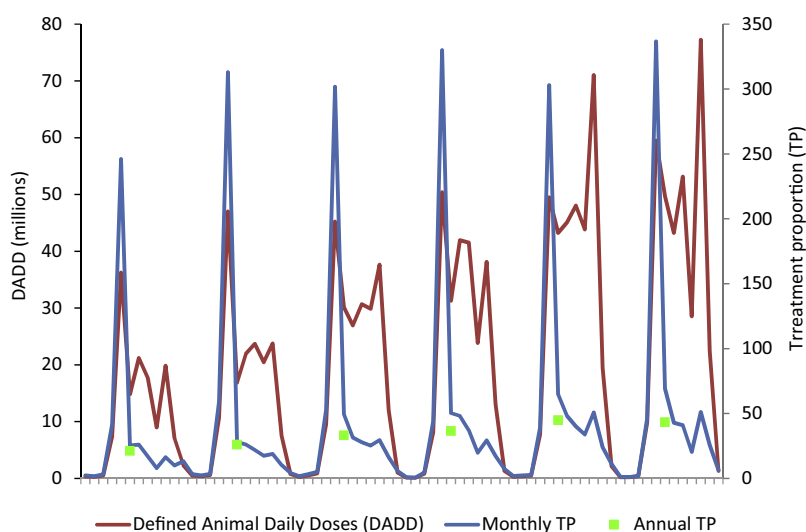
Fig. 1. Development in antimicrobial prescription for 1316 Danish mink farms during 2007–2012.Treatment proportion (TP) = number of DADD/(biomass-days), calculated over a month (monthly TP) or a year (Annual TP).
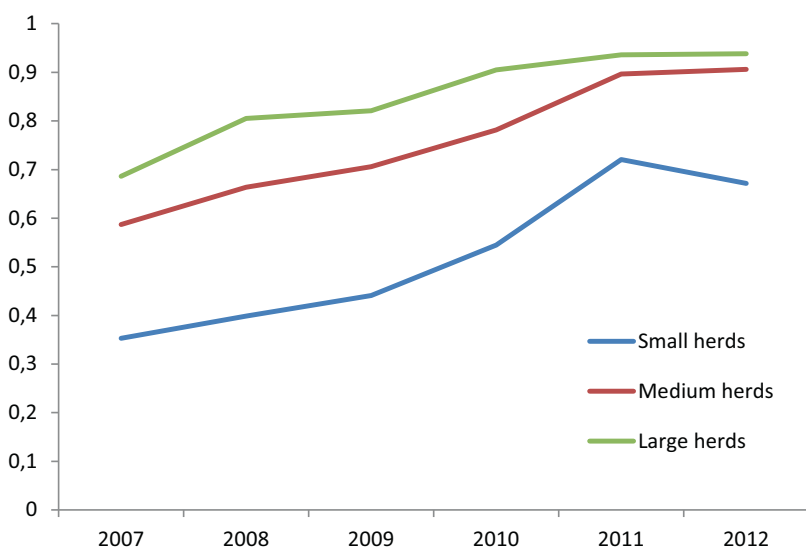

Fig 2. Proportion of 1316 Danish mink herds with antimicrobial use within each calendar year 2007–2012.

Table 2
Parameter estimates of potential explanatory variables from a multivariable binomial model of monthly antimicrobial usage in 1316 Danish mink farms, 2007–2012.

Parameter	(Pr > chi-square)	Categories	LS means parameter estimates	95% confidence interval	
				Lower limit	Upper limit
Calender year ($p = 0.004$)		2007	−2.08	−2.25	-1.92
		2008	−2.02	−2.16	−1.88
		2009	−1.78	−1.92	−1.65
		2010	−1.70	−1.84	−1.57
		2011	−1.42	−1.55	−1.30
		2012	−1.38	−1.53	−1.24
Herd size ($p < 0.0001$)		<1500 dams	−2.18	−2.33	−2.04
		1500–2499 dams	−1.65	−1.79	−1.52
		≥2500 dams	−1.36	−1.49	−1.23
Disease count[a] ($p < 0.0001$)		0	−1.94	−2.05	−1.83
		1	−1.52	−1.69	−1.37
Feed producer[b] ($p < 0.0001$)		13 levels	Estimates shown in Fig. 3		
Feed producer-year interaction ($p < 0.0001$)		84 levels	Trends shown in Fig. 4		
Vet-group[c] ($p < 0.0001$)		23 levels	Estimates shown in Fig. 3		

[a] Number of confirmed laboratory diagnoses.
[b] 13 Feed producers delivering all feed for the included mink farms.
[c] Grouping of veterinarians based on the number of farms for which they are the responsible veterinarian, see also Table 1.

Table 3
Score statistics for explanatory variables in a log-normal model of antimicrobial prescription[a] in 1216 Danish mink farms, 2007–2012.

Source	Df.	Chi-square	Pr > chi-square
Calender year	5	21.0	0.0008
Calender month	11	522	<.0001
Herd size	2	42.9	<.0001
Disease[b]	7	66.6	<.0001
Feed producer[c]	12	37.4	0.0002
Vet-group[d]	21	179	<.0001
Score[e]	1	7.5	0.006
Year × feed producer	60	123.0	<.0001
Herd size × month	22	75.1	<.0001

[a] Measured as the treatment proportion (TP—number of daily doses/biomass-days) on a logarithmic scale (log TP). Only months with antimicrobial on the farm were included, i.e., 13,479 observations of 94,752 observations (farm-months).
[b] Laboratory confirmed diagnoses.
[c] 13 Feed producers delivering all feed for the included mink farms.
[d] Group of veterinarians defined based on the number of farms for which they are the responsible veterinarian, see also Table 1.
[e] A measure of microbiological feed quality.

time. In 2007, the differences between the *feed producers* were larger than the years after. The trends for the effect of *feed producer*s over the *year*s are shown in Fig. 4.

The multi-comparison test (Šidák, 1967) showed statistical significant difference between groups of *feed producer*s. *Feed producer* a, b, and c belonged to the group with the highest values and were significant different from k, l, and m which belonged to the group with the lowest values. The rest of the feed producers were not significantly different from each other.

Concerning the veterinarians (*vet-group*), the multi-comparison test showed that veterinarian number1, 2, and 3 were significantly higher than veterinarian number 21 and 22. Veterinarian group 23 was the dummy variable for farm-years without prescription, and—as expected, had a significantly lower value than all other *vet-group*s. The rest of the veterinarians (*vet-group*s) were not significantly different from each other.

Herd size was also significant and showed that large farms receive antimicrobials more frequently.

The number of diagnosed disease outbreak (*disease count*) was significant. Going from zero confirmed diseases to one or more confirmed disease outbreak(s) increased the probability of prescriptions. However, having two disease outbreaks in a year compared to one did not further increase the frequency of prescriptions significantly over the year, possibly due to the low number of cases or submissions (two submission with confirmed disease in 8/7896 herd-years). Therefore, the disease count categories 1 and 2 were merged, changing the variable disease count into a dichotome variable in the final model.

3.2.2. The log-normal model (model B)

The log-normal model investigated the quantitative effects on antimicrobial use, but only in months where antimicrobial was prescribed. Thus, the measured effects do not represent effects on the overall antimicrobial consumption, but effects compared to other months with antimicrobial prescription.

After a backward elimination procedure, where all interaction terms less than 0.001 was removed, 3 interaction terms were significant (*year × month, year × feed-producer,* and *month × herd-size*). However, the term *year × month* gave little information of the reason for the variation. When this term was removed from the model, the variable *score* went from a *p*-value of 0.405 to 0.006; a shift in p-value was not observed for the other variables in the model. Thus, the variable *score* was able to describe the variation over the month almost as well as the interaction term *year × month*. Even though the p-value for *score* was higher than 0.001(which was our significance level) we decided to keep *score* in the final model. The final

log-normal model included the explanatory variables *year, month* (season), *feed producer, vet-group, herd size, score* and *disease* plus the interaction terms *year × feed-producer* and *month × herd-size*. The p-values for the explanatory variables are show in Table 3.

Parameter estimates for the main effects are shown in Fig. 5. Multi comparison test of the *feed producers* showed that *feed producer d* was associated with significantly larger TP, while *feed producers h* and *g* were associated with significantly lower TP compared to all other feed producers (Fig. 5A). Veterinarian (*vet-group*) 15, 1, 2, 4 and 13 were associated with a significantly larger TP than most other *vet-groups* (except 5, 7, 20, 14), while veterinarian 12 was associated with a significantly lower TP compared to the most of the other *vet-groups*, except *veterinarian* 20 (Fig. 5C). The *vet-groups* comprising veterinarians with occasional (*vet-group* 19) or regular prescription (*vet-group* 17) were grouping with all the other veterinarians, excepting the mentioned above. Multi comparison test showed that the three *herd size* classes were significantly different, with significantly lower TP values with increasing herd size. Specific diagnosed diseases (Fig. 5B) were associated with increased TP, including *P. aeruginosa*, astrovirus *Salmonella spp.* and influenza virus, in descending order, although *Salmonella spp.* was only borderline significant (*p* = 0.027). The confidence interval for no disease diagnosis "None" was narrow, whereas the confidence interval was very large for most of the diagnosis, due to the low number of diagnoses (195 observations with disease diagnoses in total, 13285 observations with no disease diagnosis). Multi comparison test showed an increased TP in May through December compared to January–April, and TPs in May and November were significantly higher compared to all other month (Fig. 5E). Finally, calendar year was significantly associated with TP, and a decrease in TP was observed from 2009 to 2011 (Fig. 5F). Multi comparison test showed a significantly lower TP during 2010–2012.

In order to examine the goodness of fit the residual plot was explored. The residual plot showed a cloud that in fact consisted of two overlaying clouds on top of each other (data not shown). The two clouds were due to the ways of prescribing the antimicrobial, either by parenteral administration or by oral administration. Thus, the administration route may be interpreted as an explanatory variable for the outcome variable, TP, because it explains some of the variation observed in TP. Oral administration was generally associated with larger TP values (higher response values in the model), and parenteral administration was generally associated with the lower TP values. However, the outcome of interest in this model is the amount of prescribed antimicrobial per animal (TP), as an indicator of morbidity (or possibly metaphylaxis). Thus, because the extent of morbidity is likely to determine whether parenteral or oral treatment is chosen, the administration route becomes part of the outcome of interest. Additionally, other parameters, e.g., veterinarians, were likely to have some degree of confounding with administration route. Therefore, including administration route would partially hide the effect of other parameters on the outcome of interest. Thus, it was decided not to include administration route in the final model, even though the residuals show a weak pattern (two overlapping clusters, both with random distributions). As the residuals formed the two overlapping clouds the residuals were not completely normal distributed; however, variance analysis is robust to some departure from normality especially when the data set is large (Khan and Rayner, 2003).

To explore the effect of not including administration route, we carried out additional analyses firstly by including administration as an explanatory factor; and secondly, by performing the analysis on two separate data sets: TP in months with parenteral prescription only and TP in months with oral use. The most interesting findings in these analyses concerned the effects of disease: In both models, Astrovirus, Influenza and *P. aeruginosa* outbreaks were significantly associated with TP. In the final model (without the
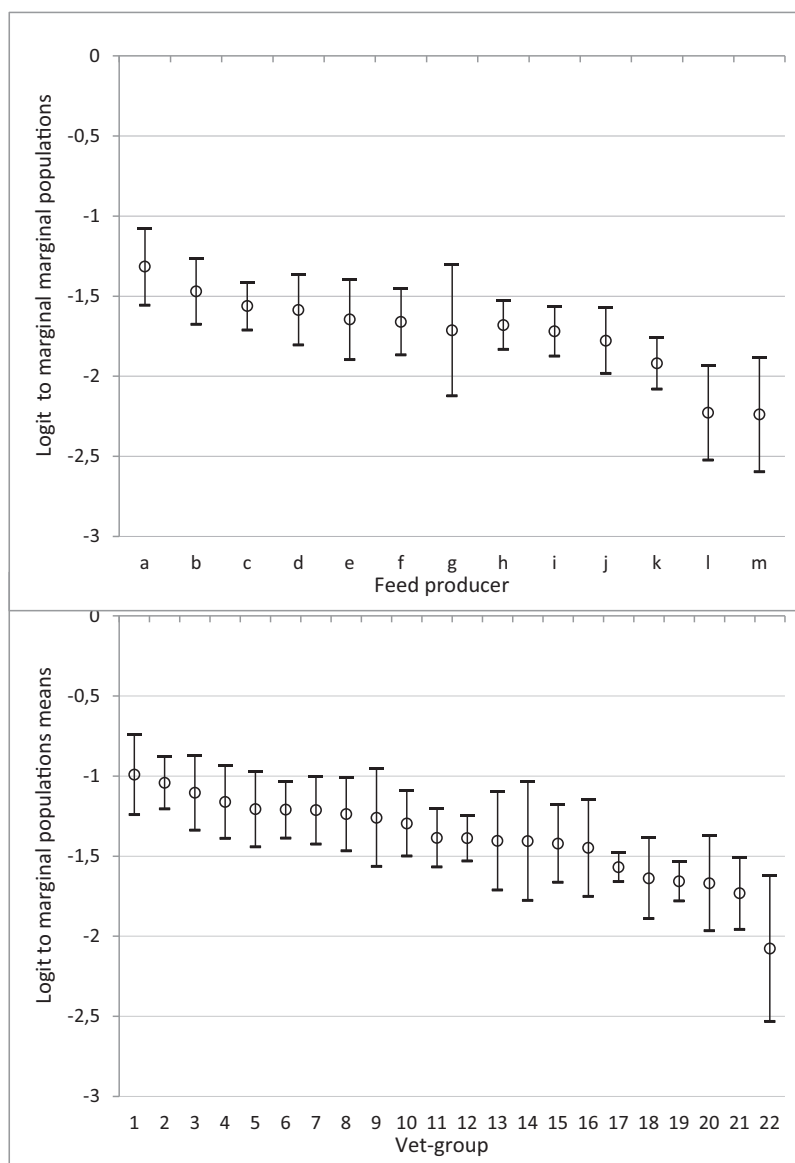
Fig. 3. Model A. Estimated effects of feed producer and veterinarians on frequency[a] of antimicrobial prescription in 1316 Danish mink farms, 2007–2012.
Vet-group: defined in Table 1 and in the text. The dummy-vet-group "no prescriptions" has been taken out of this comparison. (a) Months with antimicrobial use per year.

administration route), *Salmonella spp.* infection ($n = 21$) was borderline significant ($p = 0.027$). However, when administration route was taken into consideration, the effect of *Salmonella* infection dissolved, and MEV (parvovirus) infection ($n = 13$) was found to have a significant effect ($p = 0.004$) on oral treatment.

3.3. Comparison of grading of veterinarians and feed producers in the two models

The comparison of the ranking of feed producer in the two models (i.e., in respect to frequency and the amount of antimicrobial use in months with prescription) is shown in Fig. 6. A correlation analysis showed a significant association between frequency and amount within feed producer ($p = 0.046$).

For the *Vet-groups*, there was no significant correlation between frequency and amount of prescribed antimicrobial (Fig. 7).

4. Discussion

The results of the two models must be interpreted with caution and should be considered complementary. Neither of the models

analyzes the effects of the explanatory variables on the overall consumption of antimicrobial consumption: The binomial model was used to identify variables that increase the probability of (monthly) prescription but gives no information on the amount of antimicrobial prescribed. The log normal model is quantitative and analyzes the treatment proportion, i.e., the amounts prescribed relative to the biomass (on a monthly basis) as the outcome variable. However, as the months without antimicrobial prescription had to be omitted, the outcome variable was a measure of the magnitude of prescription only within months with prescription.

I Denmark, all veterinary antibacterial medicines must be prescribed by a veterinarian on the basis of diagnosed disease in the animal or herd. In the mink production, the most common indication given by the veterinarian on the prescription was gastrointestinal disease, while in autumn, respiratory disease is also common (VetStat prescription data). Diarrhea may be caused by specific pathogens, which may be verified by a laboratory diagnosis or may be caused by unspecific causes, including opportunistic pathogens. When an outbreak of ADV, CDV, or *P.aeruginosa* are diagnosed, the farmer may be compensated for the loss by
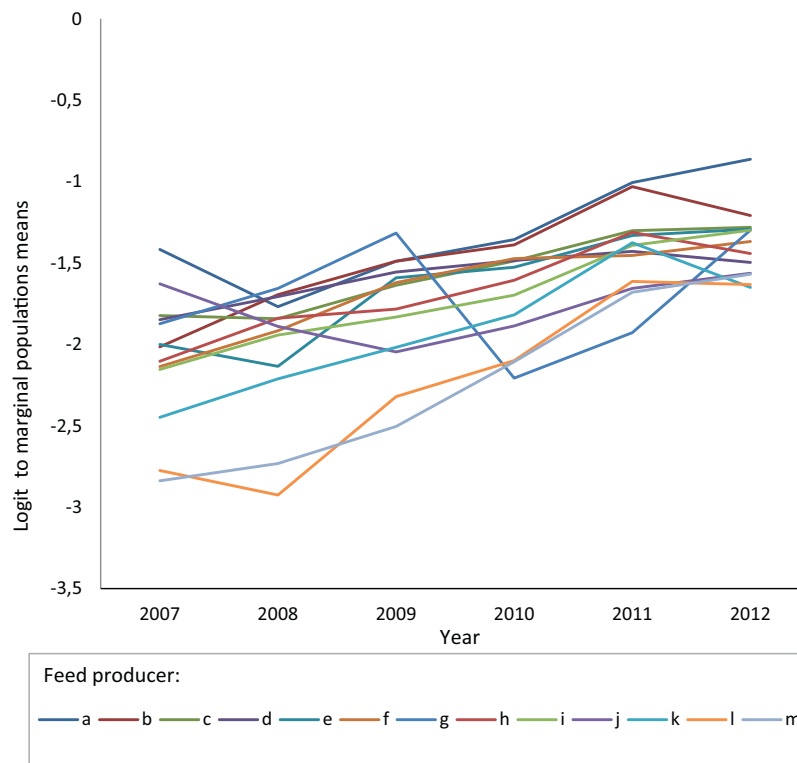
Fig 4. Trends in parameter estimates for the effect of feed producer on the use of antimicrobials in 1316 Danish mink farms during 2007–2012. Based on the estimates for the interaction term in the binomial model (Model A).

Kopenhagen Fur, given that the diagnosis has been verified on a laboratory approved by the Danish Veterinary and Food Administration (Anon., 2015b). In Denmark, the NVI and Kopenhagen Diagnostics (only ADV) (Kopenhagen Fur) are the only approved laboratories for this task. Therefore, the laboratory data included in this study can be assumed to have a very high coverage for CDV and *P. aeruginosa*. Consequently, the estimated effects of these diseases are relatively solid, with a highly significant effect of *P. aeruginosa* and no effect of CDV on antimicrobial use. Regarding ADV, the included data represent only about 10% of the diagnosed cases, as the majority is tested at the laboratory at Kopenhagen Fur.

In this study, the incidence of specific disease diagnosis was low, with a positive laboratory diagnosis (at NVI) in only 1.4% of the observations (Model B). In particular, MEV and *Salmonella spp.* was diagnosed at the NVI in very few instances. Consequently, very large confidence intervals were observed for the parameter estimates. Common infections like astrovirus (Englund et al., 2002) were most likely considerably underdiagnosed in this study. For MEV, the data included only 13 observed cases, and no significant effect on TP was observed in the final Model B. However, MEV was a significant factor for TP when administration route was taken into consideration, increasing the statistical power, because MEV was mainly observed in months with oral use. Furthermore, the undiagnosed cases associated with antimicrobial use add to the general level of antimicrobial use in this study herds, and consequently the observed effects of specific underreported pathogens like astrovirus, influenza virus, salmonella and MEV were most likely underestimated in this study. For example, much of the diarrhea treated in the pre-weaning period in May–June is associated with astrovirus, but represented by the seasonal effect (month) in the models.

Disease occurrence commonly has a seasonal pattern. In this study, a significant effect on amounts of antimicrobial prescribed in specific months was found. The high parameter estimates for May

and November indicate that in these months larger amounts are being prescribed per animal, indicating longer treatment courses and/or larger proportion of the animals. In contrast, the low parameter estimates for January-March indicate that when the breeding stock was treated in the winter, a smaller proportion of the animals (more parenteral treatment) and possibly shorter treatment courses were applied.

This study demonstrated a significant effect of "feed producer", indicating an effect of feed quality on animal health and possibly spread of specific pathogens through the feed; albeit other unknown factors confounding with the feed producer cannot be ruled out. Specific pathogens like influenza virus originating from pigs may be spread with the feed (Chriél et al., 2010). Low quality of feed, with high bacterial count and high ammonia level may cause unspecific diarrhea. Some feed producers were associated with a high prescription frequency (Model A), and some (not necessarily the same) were associated with large amount of antimicrobial prescribed (Model B). The correlation test showed a significant association between frequency and amount ($p = 0.046$), suggesting that some feed producers were associated with an overall higher antimicrobial use on the connected farm. In both models, *feed producer* and the interaction term *year × feed producer* were significant, i.e., the effect of feed producer changed over time, suggesting that the feed quality varies over time within feed producer. The feed quality score was found to be significant in the log-normal model (model B), i.e., explaining much of the monthly variation (on monthly prescription) that was not explained by other factors. However, *Score* only represents 4 microbiological parameters, i.e., total bacterial count, sulfide producing bacteria, enterococci and mold. This study suggests that other feed quality parameters are important for the occurrence of disease, as feed producers were highly significant for antimicrobial prescriptions in both models.

This study also demonstrated effects of other parameters with no obvious association to disease occurrence, i.e., the effects of
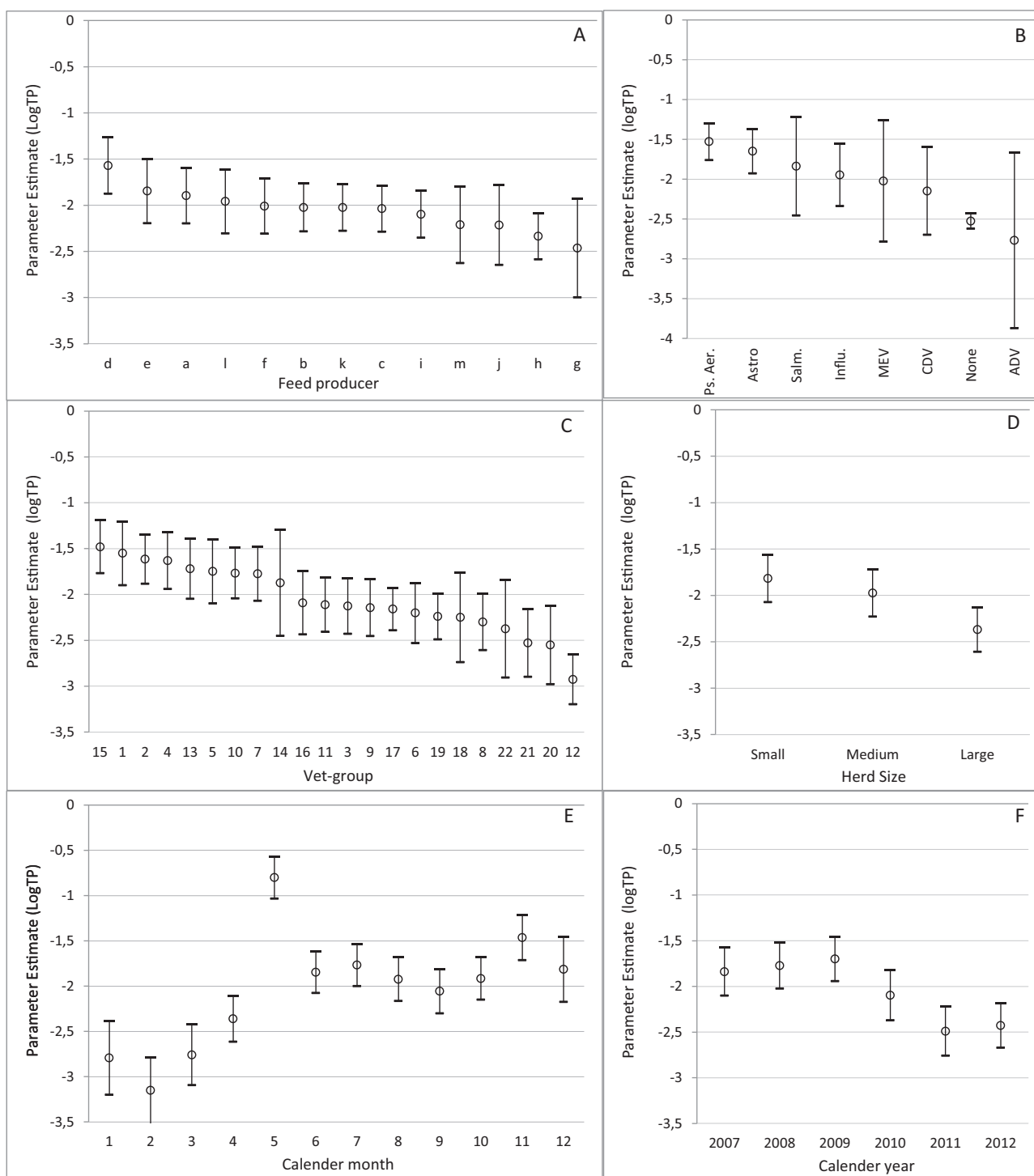
Fig. 5. Model B. Parameter estimates for effects on the antimicrobial treatment proportion (TP) on herd level[a] for 1316 Danish mink farms during 2007–2012. The variables are described in Section 2.4.1. Disease—confirmed laboratory diagnosis of the infections, Ps. Aer.—Ps. aeruginosa, Astro—astrovirus, Salm—*Salmonella* spp., Influ—influenza virus, MEV—mink enteritis virus, ADV—aleutian disease virus, CDV—canine distemper virus. (a) In months with antimicrobial prescription.

herd size, *year* and veterinarian (*Vet-group*). The descriptive analysis showed an increasing trend in amounts of antimicrobial prescribed over the study period, with more than doubling in number of DADD/kg biomass-days (national TP) across the study period. An increasing trend with time was also observed in the binomial model (model A), indicating that the prescribing of antimicrobial occurred more frequently (more months/year). In contrast, a negative estimate for *year* was obtained in the log-normal model (model B). This could be explained by an increased frequency of prescription of par-

enteral medicines in month without oral treatment, as parenteral treatment usually includes fewer animals (lower TP). The observed increasing trend in total antimicrobial use across the study period also coincided with an increase in the proportion of farms receiving antimicrobials; previously, many farms, particularly the small farms did not receive antimicrobials at all (Fig. 2).

Calendar year in itself is not an explanatory parameter, but must be explained by other factors not accounted for in the models. Potential explanations must therefore be sought in factors or inci-
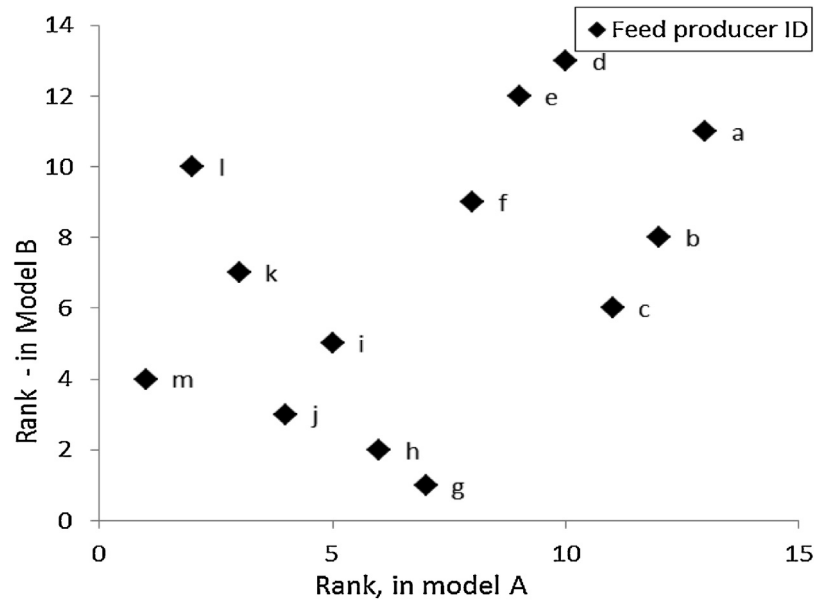
Fig 6. Comparison of ranking of Feed producer by estimates for effects on antimicrobial use in 1316 Danish mink farms, 2007–2012.
Increase in ranking represent an increase in frequency (*X*-axis) or treatment proportion (*Y*-axis)Model A: binomial model. Antimicrobial prescription measured as proportion of months with antimicrobial use. Model B: log-normal model: measurement of antimicrobial use measured as TP in months with prescription.
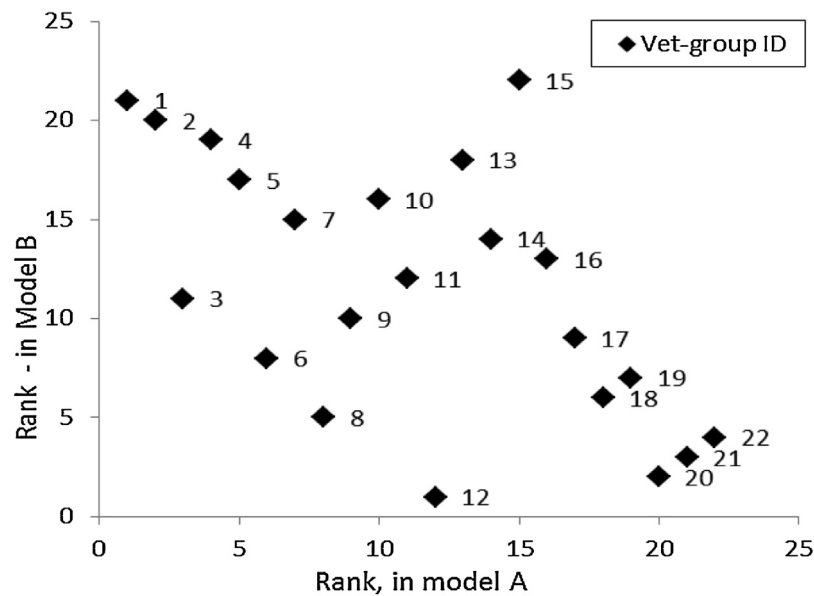

Fig. 7. Comparison of ranking of veterinarian (vet-group) by estimates for effect on antimicrobial use in 1316 Danish Mink farms, 2007–2012.
Increase in ranking represent an increase in frequency (*X*-axis) or treatment proportion (*Y*-axis). Model A: binomial model. Antimicrobial prescription measured as proportion of months with antimicrobial use. Model B: log-normal model: measurement of antimicrobial use measured as TP in months with prescription.

dents coinciding with the changes over time. The major increases in antimicrobial use were observed from 2008 to 2009 and from 2010 to 2011, both related to increasing prescription for oral use. The increase in proportion of herds treated was particularly prominent from 2010 to 2011. Also, the increase in prescription frequency was higher from 2010 to 2011 (34%), compared to other years (around 20%). It is likely, that the changes in 2011 were related to an increase in number of veterinarian visits per year, as a result of the implementation of mandatory herd health visits four times annually. This legislation was implemented early on in 2011, after official control in 2010 documented impaired health problems in some farms visited by the Veterinary Food and Drug Administration. The descriptive analysis showed that the increase in parenteral treatment was high (23%) from 2009 to 2010, suggesting

that there was actually an increase in attention to the individual animal in (temporal) relation to the debate in 2010 leading up to the legal intervention. Also, a very high increase (tripling) of parenteral treatment frequency during 2009–2011, suggests an increasing attention to the individual animals. However, in absolute numbers, the increase in oral treatment was 45 times larger than the increase in parenteral treatment during the same period (2009–2010), because oral treatment constitutes 98% of antimicrobial use (measured in DADD).

Herd size. In the log-normal model (model B), an increase in the parameter estimates was found for decreasing herd size, i.e., larger amounts of antimicrobial per animal was prescribed in smaller farms than in larger farms, in months with prescription. An exception from this was in July, when the highest estimate was found

for large herds (significant interaction term *month* × *herd-size*). In the binomial model (model A), the parameter estimates decreased with decreasing herd size, showing less frequent prescription in smaller farms. Taken together, the results indicate that in smaller farms, prescription takes place less frequent, but when prescription takes place, more antimicrobial is prescribed. This could be related to package size, as the smallest package size may often be too large for a treatment course, particularly in smaller farms, and leftover antimicrobials may be used in following months. A likely explanation for the partial reversal of the pattern in July could be that most herds receive antimicrobials in July for the treatment of the litters, and apparently, large herds tend to treat the litters more.

A significant effect of the veterinarian (*vet-group*) was found in both models, but no significant correlation was found between the rankings in the two models. However, the ranking indicates that some veterinarians were responsible for a significantly higher overall antimicrobial use on the farms, as they ranked high in both models. Some of the veterinarians had a pattern of frequent prescribing (Model A) of relatively small amounts (Model B), while for other veterinarians, the opposite pattern was noted. Neither of these patterns is indicative of a particularly high- or low- antimicrobial consumption in the associated farms. However, some of the veterinarians (#20, 21, 22) had lower estimates than other vets in both models, indicating that they both prescribed less frequently and prescribe lower amounts when prescribing.

5. Conclusion

In the mink production, antimicrobial use has a clear seasonal pattern, with high treatment proportions in the month of May-August due to treatment of the pre-weaning and weaning mink in a large proportion of the farms. In autumn, the crude antimicrobial consumption is moderately high, most likely due to outbreaks of respiratory disease in some herds. In accordance, month was found to have a significant effect on antimicrobial use on herd level. Other parameters that may be associated with disease occurrence were found to have significant effects on the pattern of antimicrobial use in Danish mink herds: *feed producer*, feed quality microbiological *score*, and the occurrence of some specific contagious diseases (*P. aeruginosa*, Astrovirus, Influenza virus and *Salmonella spp.*).

Low microbiological feed quality summarized in the *Score* (including total bacterial count, sulfide reducing bacterial count, mold and yeast) was associated with increased use of antimicrobial in the same month. For feed producers, there was a positive association between ranks in the two models, supporting that the extent of antimicrobial usage on farm level clearly depends on the associated feed producer. The effect of feed producer is likely due to other feed quality measures (or feed composition) not covered by the microbiological *Score*. The effects of specific feed parameters are investigated further in a current study. To our knowledge, this is the first field study demonstrating an effect of feed quality on antimicrobial use in livestock production.

Smaller herd size was associated with more infrequent prescription and larger monthly prescription (in TP) in months with prescription; this was likely an effect of package size, as prescriptions in one month may cover the need for treatment in several months in small herds. It should be further investigated if large package sizes may induce increased antimicrobial use – particularly in small herds.

In the Danish mink production, antimicrobial use increased by 102% from 2007 to 2012, particularly from 2008 to 2009 and from 2010 to 2011. The observed effects of time (year) as well as veterinarians have no obvious association with disease occurrence. Some of the veterinarians were associated both with frequent antimicrobial use and high antimicrobial use per animal in individual months indicating a significantly positive effect on overall amounts of antimicrobial used, whereas the opposite was observed for some other veterinarians. The increase in antimicrobial use over time may be a result of an increased focus on welfare and treatment of the individual animal or a lowering of the threshold for treating disease; the latter may have the side effect of increased growth and fur value.

Differences in focus on welfare/individual treatment and differences in threshold for treatment may also be explanatory for the observed effect of veterinarian. The major increase in oral antimicrobial use from 2010 to 2011 coincided with the implementation of mandatory regular veterinary visits; the increase in frequency of prescription and an increasing proportion of farms using antimicrobials may be a direct effect of increased frequency of veterinary visits. A major increase in parenteral antimicrobial use occurred in 2010, suggesting an increased focus on treatment of the individual animal; this coincided with an intense public debate on welfare in the mink production. However, this study does not provide documentation of causality in regard to the overall increasing antimicrobial use over time.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.prevetmed.2016.01.023.

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