Influence of demographic factors on antibiotic prescription behaviour of veterinarians

Danique Bens

4073991

Supervisor: David Speksnijder

Index

1. Abstract
The prevalence of multidrug-resistant organisms and the infections caused by these are rising while on the other hand development of new lucrative therapeutic area by pharmaceutical companies is abandoned. Therefore, rigorous strategies are necessary to preserve the valuable and still working antimicrobials for next generations. In order to understand the role of antimicrobial resistant (AMR) bacteria in veterinary medicine, improved monitoring of antibiotic use in food-producing animals is already implanted. Only monitoring antibiotic use is not enough to understand the motivation behind prescription behaviour of farm animal veterinarians, which is vital to identify potential key motivators and barriers to enhance a more prudent antibiotic use. In this study the influence of demographic factors on prescription behaviour are analysed. A large dataset on demographic factors on personal level, like gender, employment status, place of graduation, year of graduation and on practice level, like postal code area, is made with the use of public data. (n=1077) An other demographic factor is type of practice, which is collected with the use of an online survey. (n=1055) These datasets are analysed for possible relationship between the demographic factor and prescription level.

Significant difference in prescription level are found 3 years in a row on the individual demographic factors gender (cattle veterinarians) and place of graduation (pig veterinarians). On practice level the practice itself, the postal code area and type of practice significantly influence prescription behaviour of veterinarians.

Keywords; livestock, prescription behaviour, veterinary, demographic factors, antibiotic use, prudent use

2. Introduction

2.1 History of Antibiotics

Throughout most of the time in human history, herbal and folk medicine were the only available remedies for therapy. However, when affected by an infectious disease, this treatment was often insufficient and could lead to serious illness or death. At the end of the 19th century, Robert Koch and Louis Pasteur discovered the existence of microbes and demonstrated their pathogenicity in animals for several recognized diseases including cholera and anthrax (Quinn et al., 2011). This revolutionary identification, regarding the reason of infectious disease, provided a target for healing treatment. Ehrlich made the first steps in the golden antibiotic age by discovering the selective bind of aniline dye molecules with bacteria. He initiated the search for a 'magic bullet' against bacteria and inspired multiple ground breaking studies. In 1932, Gerard Domank found that sulfamidochrysoidine, a derivate of sulphanilamide, protected against staphylococci and streptococci (Dodds, 2017; Strebhardt & Ullrich, 2008). A second revolution in the discovery of antimicrobial treatment was the serendipitously discovery of penicillin by Alexander Flemming in 1928, but problems with stability and purification of the active compound made it unusable clinically (Fleming, 1929). Antibiotics were introduced into medical practice by the synthetic drug sulphonamide in the 1930s followed by penicillin and streptomycin in the 1940s . The range of antibiotics was expended by broad spectrum bacteriostatic antibiotics in the 1650s and antibiotics with bacteriocidic function in the 1960s. The discovery of antibiotics is often called the greatest medical triumph of the 20th century (Komolafe, 2003). Antibiotics were introduced almost parallel in animal healthcare in the 1950s, initially as curative measurement for diseases. Later on they were also implied as preventive measurement and antimicrobial growth promoter (AGP) to improve animal production (Van den Bogaard & Stobberingh; 1999; Stockstad 1950).

2.2 Policies on antibiotic use

The potential risk of resistance against antibiotics was already described by Fleming in 1945 (Alanis, 2005). However, the increasing social and scientific stimulation for prudent use of antibiotics nowadays, both in veterinary and human medicine, is a result of expanded occurrence of Antimicrobial resistance (AMR) globally. Infections with multidrug resistant bacteria result in increased morbidity and mortality merged with higher social and economic costs (Cosgrove, 2006).

In 1969 the first international body raised awareness for the excessive veterinary use of antibiotics in combination with increasing resistance levels and the potential impact for human healthcare. (Swann et al. 1969) Notwithstanding these serious concerns and increasing knowledge about veterinary antibiotic use, it took until 1986 when Sweden was the first country to ban all antimicrobial growth promoter (AGP) as precautionary measurement (Wierup, 2001). In 1995, the Danes withdrew the use of AGP avoparcin in pigs and poultry and also the European union followed in 1997 (Speksnijder et al., 2015b). Further recommendations by the world health organisation in 1997 and the Copenhagen recommendations in 1998 resulted in a ban on the use of specific growth promoters in 1999 and a complete restriction in 2006 (Barton 2000, Cogliani et al., 2011).

The inconvenience of this of this ban was a prominent increase in therapeutic veterinary antibiotics (SDA, 2018), see Fig 1. This veterinary antibiotic use in kilograms is much higher than the use in humane healthcare. In 2007, the Netherlands was even ranked as the highest veterinary antibiotic consumer out of 10 European countries with data (Grave et al., 2010). Resistance levels in livestock associated bacteria were reported in 2005 with a methicillin resistant *Staphylococcus aureus* in pigs. Later an extended spectrum beta lactamase producing bacteria was found in poultry meat in 2009. This led to serious public involvement and concern, followed by a debate in parliament (Leverstein-van Hall et al., 2011; Voss et al., 2005). The extensive use of antibiotics in farm animals was thought to contribute to the overall antibiotic resistance and it would maybe represent a risk for human health. Therefore, the government introduced a reduction target of antibiotic use in farm animals of 20% in 2011 and 50% reduction in 2013 in comparison with 2009. In 2013 the government set a new goal of 70% reduction in veterinary antibiotic use in 2015 (Speksnijder et al., 2015b). The SDa reported a 63,8% reduction in the antibiotic use in farm animals in the period 2009-2018 (SDA, 2019).

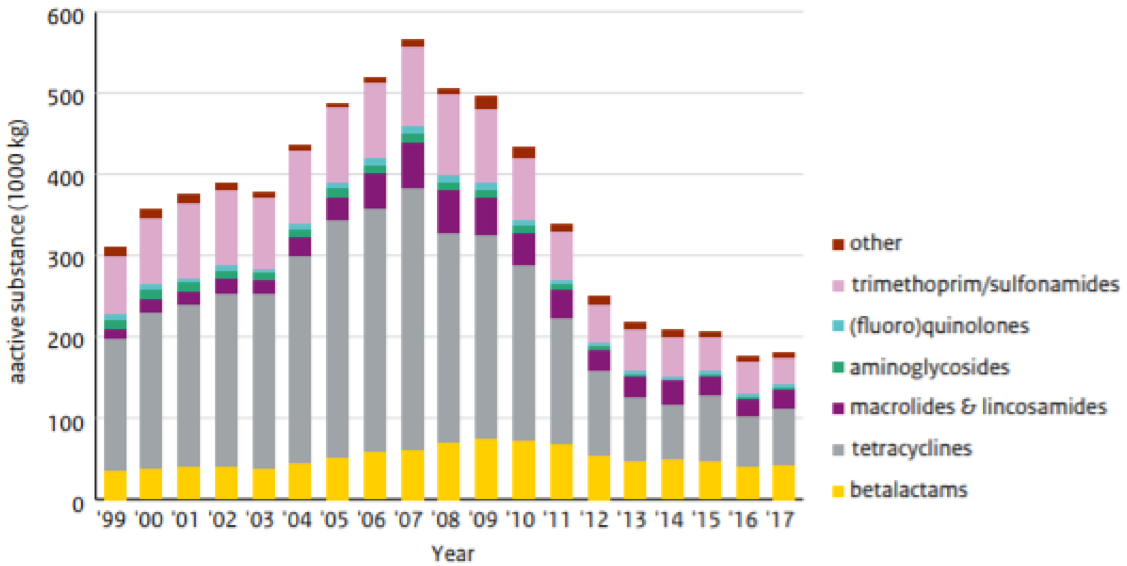


Figure 1. Development in sales of antibiotics. Period 1999-2017 (SDA, 2018)

2.3 Benchmarking authorities

In 2010 the Netherlands Veterinary Medicines Authority, SDa, was established by the Dutch government to promote prudent drug use in animal husbandries (Speksnijder et al., 2015b; SDA, 2014). The main focus point was decreasing the use of antibiotics and thereby reduce public health risks. Until then it was only possible to monitor antibiotic use on national level and now it was possible to monitor the use of antibiotics on farms and veterinarian level. Thereby, it was also possible to benchmark and differentiate between low, moderate and high prescribers (veterinarians) and users (farmers). Disciplinary sanctions could be subjected based on these datasets (SDA, 2014).

Prescription data of veterinarians is recorded in Practice Management Systems (PMSs) and subsequently transferred to central sector databases. From the collected data, it is possible to calculate the defined daily dose animal (DDDAf) on a livestock farm. At a particular livestock farm the treatable kilograms are divided by the average total kilograms present in order to create this parameter (SDA, 2018). With the data the SDa is able to set two benchmark values defining 3 zones; A target, signalling and action zone. These zones are divided by a signalling threshold and an action threshold for each livestock sector. These benchmarks are evaluated each year by the SDa expert panel.

In the Netherlands, farmers have a compulsory one-on-one relationship with a veterinarian. The veterinarians share the farmers responsibility for their animals, and in context of resistance, also for human healthcare. In order to reflect a particular veterinarian's prescription pattern, and identify inter-veterinarian variability in these patterns, a veterinary benchmark indicator (VBI) is calculated. The range of this parameter is 0-1 and reflects on the probability of a 1-1 relationship of a veterinarian with an action zone livestock farm. A VBI of 0.15 means that 15% of the one-on-one relationship farms of a veterinarian is in the action zone.

For this study the DDDAvet is determined by first calculating the total number of treatable kilograms prescribed by a particular veterinarian in a year and secondly divided by the average number of kilograms of animals present on all farms with a registered one-to-one relationship with the veterinarian. A veterinarian who works with different livestock species, has a unique DDDAvet for each group (SDA, 2018).

2.4 Influences on antibiotic use in farm-animals by farmers and veterinarians described in literature

Different actors, such as veterinarians, farmers, other farm advisors and health authorities, are involved in the use of antibiotics. In Europe, antibiotics are medications which must be sold under medical prescription. Therefore, veterinarians could be a fundamental target for any action aimed at improving the prudent use of antibiotics. As a preliminary step in designing effective antimicrobial stewardship interventions, better knowledge is needed about the determinants that influence antibiotic prescription behaviour of veterinarians.

Species related

National defined daily dosages (DDDAnat), in the largest sectors of food production animals in the Netherlands, show a difference in antibiotic use between the sectors. Turkey and veal calves provide the highest rates, with daily doses above 20 per animal year, see figure 2.

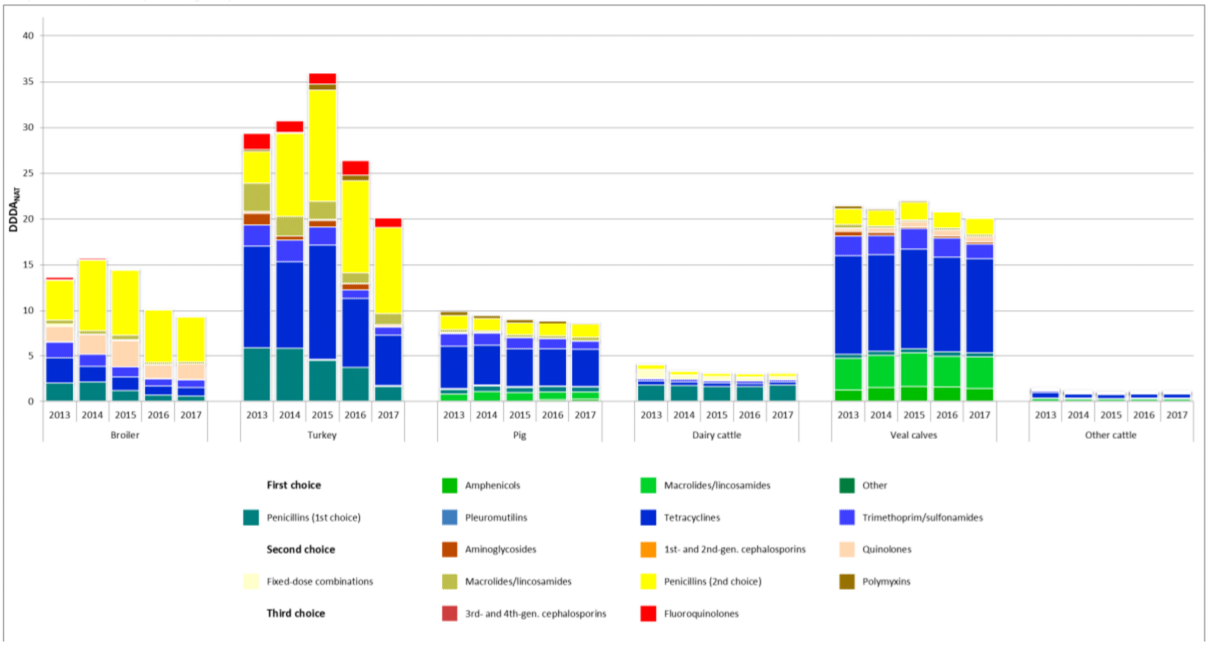


Figure 2. National DDDAvet scores by livestock sector. Period 2013-2017

Veterinarians

Prescription behaviour of physicians in the Netherlands is known to be influenced by several factors. Internal factors related to personal attitude and knowledge but also external factors as policies and patient influences play a role in this context. In food producing animals, veterinarians are responsible for the prescription of antibiotics. However, limited information on prescription behaviour is available to identify potential key motivators for prescription behaviour of farm animal veterinarians in the Netherlands. Factors which influence prescription of antibiotic are the use of sensitivity tests, that are described in literature are the use of sensitivity tests, own experience, risk of AMR and the ease of administration (de Briyne, 2013). Other studies mention a lack in practical applicable knowledge in prevention and treatment of diseases and the fear of major complications with high morbidity and mortality rates with deterioration of animal welfare in combination with economic consequences and dissatisfaction of the farmer as a reason for imprudent prescription of antibiotics. (Dean et al., 2011) Research on demographic determinants who influence prescription behaviour in veterinarians is sparse. The influence on practice level is shown in a study on dutch companion animal prescription where a significant difference between clinics was found (Hopman et al., 2019). Most of the studies related to the association between prescription behaviour and demographic factors are based on patients and not the prescribers (Vogler et al., 2015, Mayer et al., 2015; Fernandez et al., 2008).

Demographic factors

Studies in human healthcare are analysed due to the lack of studies in de veterinary field. Gender was a variable assessed by several studies where higher prescription values were associated with male practitioners (Moghadamnia et al., 2002; Lam & Lam, 2003; Chamany; 2005; Cadieux et al., 2007; Mazzaglia et al., 2003). However, other studies found no relationship between gender and antibiotic prescription behaviour (Pradier et al., 1999; de Sutter, 2001; Cho & Kim, 2002; Akkerman et al., 2005; Cotter en Daly, 2007). The relationship between years in practice and antibiotic prescription is also described in literature; There are articles who found a positive relationship, while others found an negative or even no relationship (Kuyvenhoven et al., 1933; Carr et al., 1994; Watson et al., 1999; Lin et al., 2000; Lam & Lam, 2003; Fakih et al., 2003; Thope et al., 2004; Teng et al., 2004; Chamany et al., 2005; Finkelstein et al., 2005; Akkerman et al., 2005; Fischer et al., 2005; Bharathiraja et al., 2005; Cadieux, 2007). An influence of geographic location of the practice on antibiotic prescription is also reported (Mazzaglia et al, 2003; Bhatnagar et al., 2003; Huang et al., 2005). Finally, also differences in institute of graduation is investigated in 2 studies (Cadieux et al., 2007; Lam & Lam 2001).

3. Aim, outline and social relevance of thesis

Only monitoring antibiotic use is not enough to understand the motivation behind prescription behaviour of farm animal veterinarians, which is vital to identify potential key motivators and barriers to enhance a more prudent antibiotic use.

The aim of the study is to investigate factors associated with high or low prescription behaviour of farm animal veterinarians in the Netherlands. Therefore, extended research into socio-demographic factors were analysed in order to confirm a possible relationship. The research question in this study is at follows; which demographic factors of farm animal vets are associated with prescription behaviour? Sub questions are summarized in table 1.

Table 1. Research questions and selected statistical tests

Research question - poultry, veal calves, pigs and cattle
<u>Open data</u>
1a.Does antibiotic prescription behaviour of male and female significantly differ from each other?
1b.Is there a difference in male-female ratio between the lowest <35 (n) and highest > 65 percentile of antibiotic prescription
2a. Does antibiotic prescription behaviour significantly differ between alumni from Utrecht and Ghent?
2b. Is there a difference in alumni Utrecht-Alumni Ghent ratio between the lowest <35 (n) and highest > 65 percentile of antibiotic prescription?
3a. Does antibiotic prescription behaviour of (co)-owners and employees differ from each other?
3b. Is there a difference in (co-)owner : employee ratio between the lowest <35 (n) and highest > 65 percentile of antibiotic prescription?
4. Do relationships exist between the year of graduation and antibiotic prescription?
5. Does antibiotic prescription differ significantly across postal code areas?
6. Does antibiotic prescription differ significantly between practices?
7. Is there a correlation between high and low prescription behaviour between livestock species per individual veterinarian?
<u>Questionnaire</u>
8. Is there a difference between mixed practices and livestock practices?

9. Is there a difference between fulltime or parttime veterinarians?

Results of the study should gain a better insight into the prescription behaviour of veterinarians. Factors recorded which influence prescription behaviour can be helpful to adapt policy for further antibiotic reduction in the Netherlands.

4. Subjects and methods

Design

A study has been set up to gain insights into prescription behaviour of farm animal veterinarians. The used data has been obtained as part of a larger study into critical success factors for reduction of antibiotics in farm animals and is commissioned by the Ministry of Economic Affairs.

Data

Data is derived from different sources that were combined for this study. DDDAf scores originate from national sector data banks who collect scores for benchmarking. Also 1-1 relationships are collected with the help of these data banks. A DDDAvet could be calculated with the use of these data. DDDAf scores from January 1st 2014 until 31st of December were used to minimize the influence of extremes and to get a overview on fluctuations within these years per veterinarian. Demographic data (gender, practice, location of practice, country and year of graduation and employment status) are collected through a public register of the KNMVD, Social media (Facebook, Linkedin) and personal websites of practices and a questionnaire. (Respectively N=1077, N=155). Data were connected with the use of the unique veterinarian number (UDN). In this study we looked at the DDDAvet of poultry, veal calves, pigs and cattle separately for each demographic factor.

Online survey

The self-administered questionnaire was created online and sent out using Survey Monkey. To gain insight into prescription behaviour of farm animal veterinarians, questions to asses demographic variables and variables related to knowledge, attitudes and behaviour were asked. The content for this quantitative study existed of closed questions. The link of the questionnaire was provided and promoted to all practicing farm animal veterinarians in the Netherlands trough publication in two national professional journals on December 2017. Veterinarians were asked to voluntarily fill in the survey. On the 5th of March 2018 the survey was closed. N=155.

Statistical analysis

The quantitative distribution of required data and returned questionnaires are expressed by descriptive statistics (frequencies, mean SD and range). The independent variables of this study are gender, type of practice, location of practice, country and year of graduation and employment status of employer or employee. The dependent factor is DDDAvet. DDDAvet and year of graduation were continuous variables, while the rest was dummy coded, see table 2. The amount of other answers than presented in table 2 are neglectable.

Table 2 Codebook nominal factors

Gender	0 = males 1 = females
Type of practice	1 = specialized practise for 1 type of farm animal 2 = practise for farm animals 3 = mixed practise
Division of work in practise	1 = < 25% farm animals 2 = between 25-50% farm-animals 3 = between 50-75% 4 = > 75%

Personal division of work of veterinarian	1 = < 25% farm animals 2 = between 25-50% farm-animals 3 = between 50-75% 4 = > 75% farm animals 5= 100% farm animals
Working days per week	1 = less than 2 days a week 2 = between 2-4 days a week 3 = 4 days or more
Postal code area of practice	10 = 1000-1499 15 = 1500-1999 20 = 2000-2499 25 = 2500 - 2999 30 = 3000-3499 35 = 3500 - 3999 40 = 4000-4499 45 = 4500-4999 50 = 5000-5499 55 = 5500 - 5999 60 = 6000-6499 65 = 6500 - 6999 70 = 7000-7499 75 = 7500 - 7999 80 = 8000-8499 85 = 8500 - 8999 90 = 9000-9499 95 = 9500-9999
Country/faculty of graduation	0= Utrecht 1= Ghent
Employment status	Co-owner = 0 Employee = 1

Anonymizing data

The use of data was permitted under strict privacy policy. Answers of the questionnaires and required data were collected externally by IDTS in Deventer though a secured connection. Personal data was deleted and the rest of the data was anonymized by IDTS. Researchers only acquired anonymized data and IDTS destroyed the data after anonymizing. Persons or practices were untraceable for the researchers. Postal code areas are derived from the first two number of the postal code to minimize the traceability.

Data selection and statistical tests

Missing data from individuals are excluded pairwise. Outliers in DDDAvet score were detected visually and removed by a stem-and-leaf and boxplot graphs. Tests were expressed by significance level. For every veterinarian, a percentile calculation was made to provide a scale from 1-100%. All DDDAvets where combined and divided percentage wise. This means that if a vet has a 45th percentile, this means that 44% had a lower DDDAvet and 55% had a higher DDDAvet. In this way the veterinarians could be subdivided in the subcategories low (<35), middle (35-65) and high (>65) and the categories low and high could be compared with the demographic data. The influence of extreme values is minimized by this step and the step is also necessary because of the non-normality of the data. Statistical analysis were performed by means of Microsoft excel and SPSS (IBM SPSS Statistics). All used test are represented in table 3. The mann-whitney test is performed on DDDAvet, the chi square test is performed on data from prescribers of the lowest(<35) and highest percentile (>65). Linear regression is performed on all percentiles to minimize the extreme values.

Table 3 used statistical tests

Research question - poultry, veal calves, pigs and cattle	**Test spss**
<u>Open data</u>	
1a.Does antibiotic prescription behaviour of male and female significantly differ from each other?	Mann whitney
1b.Is there a difference in male-female ratio between the lowest <35 (n) and highest > 65 percentile of antibiotic prescription	Chi square
2a. Does antibiotic prescription behaviour significantly differ between alumni from Utrecht and Ghent?	Mann whitney
2b. Is there a difference in alumni Utrecht-Alumni Ghent ratio between the lowest <35 (n) and highest > 65 percentile of antibiotic prescription?	Chi square
3a. Does antibiotic prescription behaviour of (co)-owners and employees differ from each other?	Mann - whitney
3b. Is there a difference in (co-)owner : employee ratio between the lowest <35 (n) and highest > 65 percentile of antibiotic prescription?	Chi square
4. Do relationships exist between the year of graduation and antibiotic prescription?	Linear regression
5. Does antibiotic prescription differ significantly across postal code areas?	Kruskall-walace
6. Does antibiotic prescription differ significantly between practices?	Kruskall-walace
7. Is there a correlation between high and low prescription behaviour between livestock species per individual veterinarian?	Chi square
<u>Questionnaire</u>	
8. Is there a difference between mixed practices and livestock practices?	Mann – Whitney
9. Is there a difference between fulltime or parttime veterinarians?	Mann – Whitney

5. Results

In 2014, 2015 and 2016 there were 911, 928 and 924 veterinarians with a unique DDDAvet score. In total there were 1103 unique veterinarians with 1 or more DDDAvet scores in the period from 2014-2016. This study examined the difference in the DDDAvet scores for different demographic groups. Results derived from public available sources are gender, place of graduation, function, year of graduation, practice and postal code area of practice, and will be presented in the first chapter *public available data*. Data derived from the questionnaire are type of practice, division of work in practice, division of personal hours and function and are described in the chapter *questionnaire.* The demographic variables were used as an independent variable and DDDAvet scores as a dependent variable. Non parametric tests were used due to the lack of normal distribution. This was analysed with the help of boxplots, stem and leaf diagrams and histograms. Significant values are bold and a *-symbol is connected (*=p<0.05, **=p<0.00).

5.1 Public available data

Gender

The number of of gender related demographic data with a DDDAvet are illustrated in figure 3 . A mann-whitney median test was used to compare the DDDAvet score for gender, because data was not normally distributed. A Mann-whitney test indicated no significant differences between female and male DDDAvet except for cattle. The level of antibiotic prescription in male veterinarians was significantly higher than female veterinarians during 2014-2016. When the number of veterinarians in the lower percentile group was compared to the number of veterinarians in the higher percentile group, a significant variation for gender was also found for DDDAvet cattle. It shows that the male-female ratio is increased in the high prescription group in comparison to the low prescription group.

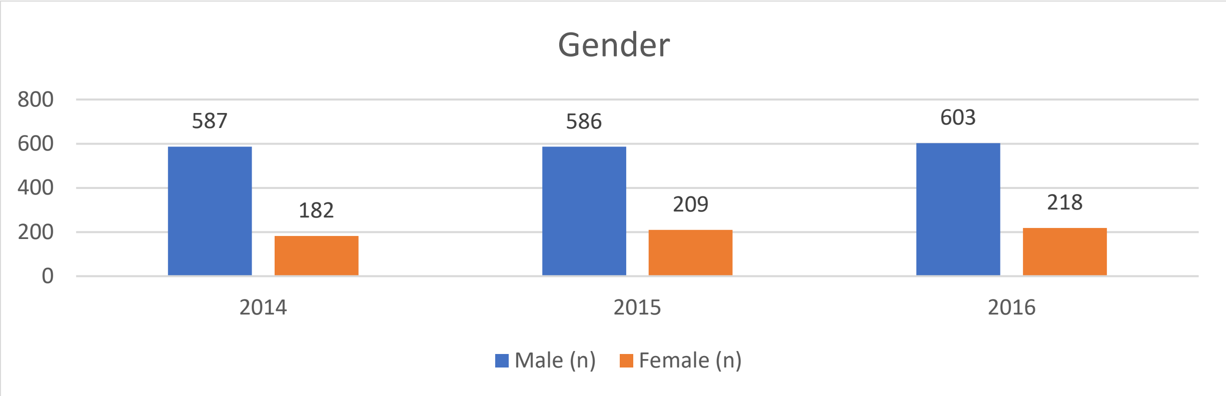


Figure 3: Number of male/female veterinarians (n) per year

Table 4: Mean DDDAvet per species and gender (mann-whitney test)

	Year	gender	N	Mean DDDAvet	SD	Mean Rank	P value
DDDAvet poultry	2014	male	47	18,78	11,62	30.63	0.336
		female	11	14,96	6,31	25.09	
	2015	male	45	14,26	8,37	31.13	0.922
		female	16	14,95	10,74	30.63	
	2016	male	47	10.71	8,39	33.00	0.721
		female	17	8.83	4,77	31.12	
DDDAvet veal calves	2014	male	105	14,69	13,04	58.40	0.571
		female	12	15,74	11,76	64.25	
	2015	male	108	14,12	14,14	61.92	0.945
		female	15	17,47	23,99	62.60	
	2016	male	102	14.71	15,67	57.51	0.392
		female	14	17.98	19,00	65.71	
DDDAvet pigs	2014	male	206	6,29	5,02	123.65	0.253
		female	36	5,19	3,11	109.19	
	2015	male	196	5,98	5,07	120.37	0.352
		female	40	5,63	5,38	109.35	
	2016	male	192	5.68	5,08	120.42	0.250
		female	43	4.87	3,33	107.21	
DDDAvet cattle	2014	male	451	2,41	1,48	312.29	**0.002****
		female	147	2,42	2,33	260.24	
	2015	male	451	2,18	1,13	323.08	**0.000****
		female	163	2,09	1,54	264.39	
	2016	male	462	2.37	2,40	331.85	**0.002****
		female	173	2.16	1.86	281.02	

Table 5. Chi-square test on lower and higher prescription percentiles

DDDAvet	Year	Gender	<35 (n)	>65 (n)	Pearson's chi square	P value
DDDAvet poultry	2014	Male	15	21	0.023	0.880
		Female	4	5		
	2015	Male	14	18	0.598	0.439
		Female	3	7		
	2016	Male	19	20	1.511	0.219
		Female	2	6		
DDDAvet veal calves	2014	Male	17	26	1.666	0.197
		Female	1	6		
	2015	Male	22	28	0.054	0.816
		Female	4	6		
	2016	Male	23	29	0.698	0.404
		Female	3	7		
DDDAvet pigs	2014	Male	40	63	5.715	**0.017***
		Female	13	6		
	2015	Male	46	57	0.419	0.518
		Female	11	10		
	2016	Male	42	51	0.928	0.335
		Female	14	11		
DDDAvet cattle	2014	Male	111	151	5.514	**0.019***
		Female	51	39		
	2015	Male	108	151	12.124	**0.000****
		Female	66	41		
	2016	Male	115	156	7.182	**0.007****
		Female	68	51		

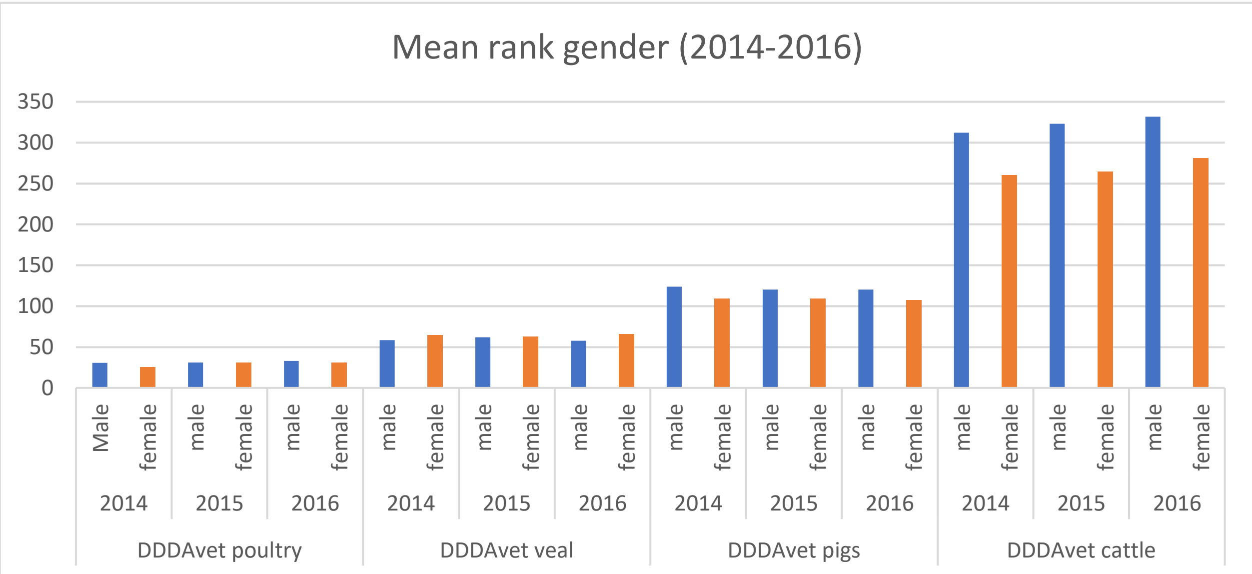


Figure 4 Mean rank DDDAvet poultry, veal calves, cattle and pigs. Period 2014-2016

Place of graduation

For place of graduation (Utrecht University vs Ghent University) the Mann-whitney difference test was utilised to illustrate the possible difference between graduation in Utrecht or Ghent. In total there were 794, 822 and 852 DDDAvets available for the alumni of these 2 Universities, see figure 5. The mann-whitney test indicated that DDDAvet pigs of alumni of Ghent (*M*=10.64, 11.27 and 10.87) were significantly higher than alumni scores of Utrecht University (*M*=5.67, 5.42 and 4.99). The data in percentiles showed the same results, were alumni from Ghent University are represented in a larger ratio in the high prescription group.

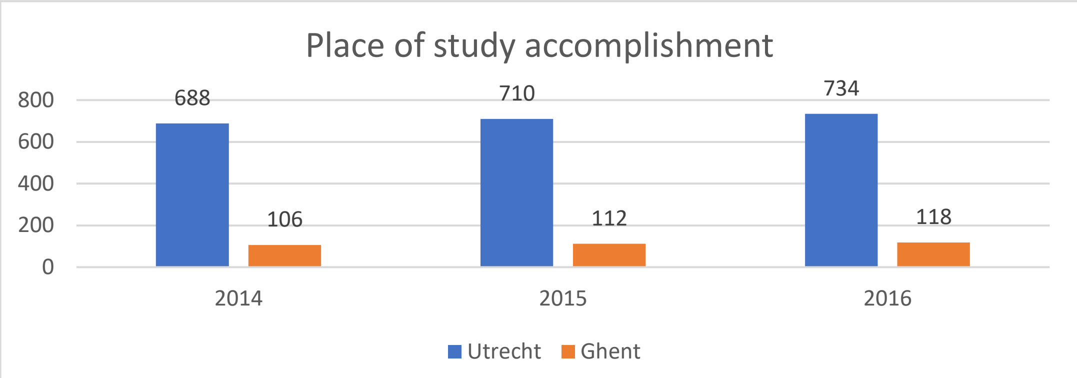


Figure 5 number of of alumni from Utrecht and Ghent. Period 2014-2016

Table 6 mann-whitney test results on factor place of graduation

	Year	Place	N	Mean	SD	Mean rank	P value
DDDAvet poultry	2014	Utrecht	51	18.14	10.90	33.65	0.329
		Ghent	13	14.90	9.12	28.00	
	2015	Utrecht	55	14.48	9.13	34.18	0.870
		Ghent	12	14.53	9.92	33.17	
	2016	Utrecht	55	10.35	7.93	35.27	0.858
		Ghent	15	10.38	6.94	36.33	
DDDAvet veal calves	2014	Utrecht	99	14.78	12.81	60.46	0.981
		Ghent	21	14.46	12.64	60.67	
	2015	Utrecht	105	13.83	14.73	61.58	0.501
		Ghent	19	18.02	19.43	67.61	
	2016	Utrecht	98	15.47	16.98	60.72	0.621
		Ghent	21	11.63	9.63	56.62	
DDDAvet pigs	2014	Utrecht	217	5.67	3.66	118.00	**0.001****
		Ghent	29	10.64	9.74	164.66	
	2015	Utrecht	213	5.42	4.35	113.86	**0.000****
		Ghent	28	11.27	8.41	175.32	
	2016	Utrecht	212	4.99	3.19	113.00	**0.000****
		Ghent	28	10.87	10.19	177.25	
DDDAvet cattle	2014	Utrecht	540	2.39	1.61	304.14	0.278
		Ghent	73	2.56	2.33	328.12	
	2015	Utrecht	553	2.16	1.30	314.86	0.343
		Ghent	81	2.37	2.07	335.53	
	2016	Utrecht	570	2.30	2.27	327.56	0.744
		Ghent	86	2.33	2.02	334.71	

Table 7 Chi square test on lower and higher prescription group for place of graduation

DDDAvet	Year	Gender	<35 (n)	>65 (n)	Pearson's chi	P value
DDDAvet poultry	2014	Utrecht	14	24	2.899	0.089
		Ghent	5	2		
	2015	Utrecht	14	24	1.907	0.167
		Ghent	4	2		
	2016	Utrecht	20	2	1.272	0.259
		Ghent	23	6		
DDDAvet veal calves	2014	Utrecht	14	27	0.340	0.560
		Ghent	4	5		
	2015	Utrecht	20	26	0.104	0.747
		Ghent	5	8		
	2016	Utrecht	21	7	0.676	0.411
		Ghent	30	6		
DDDAvet pigs	2014	Utrecht	49	56	4.313	**0.038***
		Ghent	4	15		
	2015	Utrecht	54	55	10.008	**0.002****
		Ghent	2	17		
	2016	Utrecht	54	49	14.412	**0.000****
		Ghent	1	18		
DDDAvet cattle	2014	Utrecht	148	166	0.680	0.409
		Ghent	20	29		
	2015	Utrecht	156	166	0.436	0.509
		Ghent	24	31		
	2016	Utrecht	167	22	0.652	0.420
		Ghent	185	31		

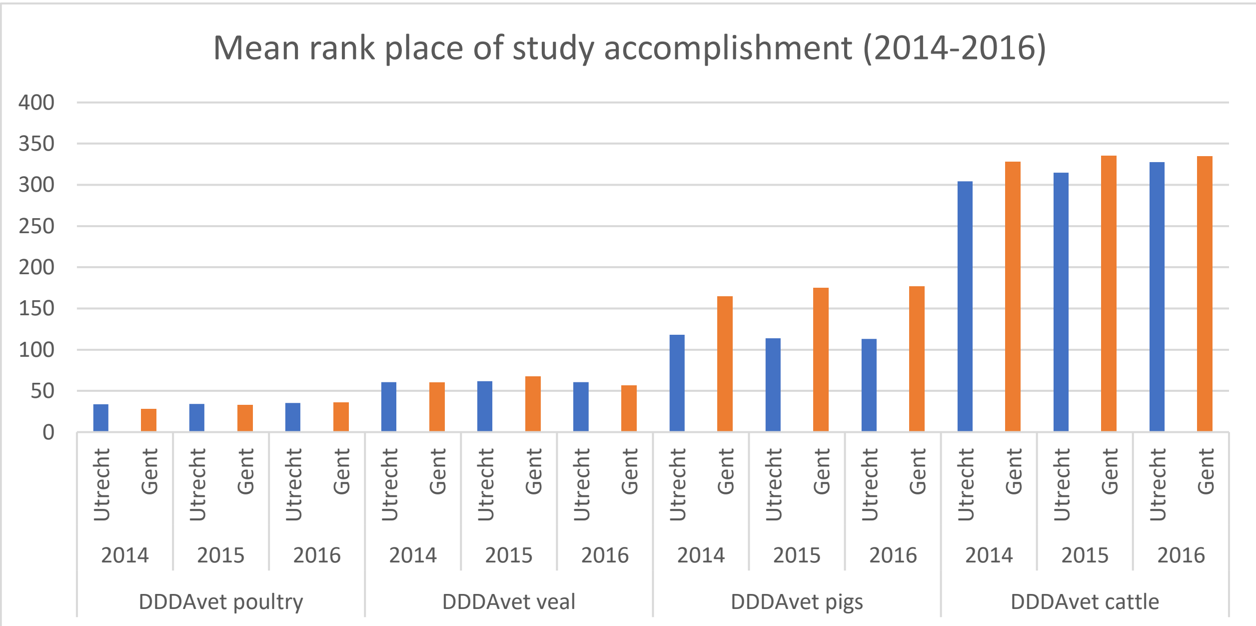


Figure 6 mean rank in place of study accomplishment. Period 2014-2016

Employment status

The employment status combined with the DDDAvet could be assessed for 619, 625 and 623 veterinarians in 2014, 2015 and 2016, see figure 7. When the DDDAvet per livestock specie was compared to the employment status, no significant difference was found except for cattle in 2015, see table 8 and 9.

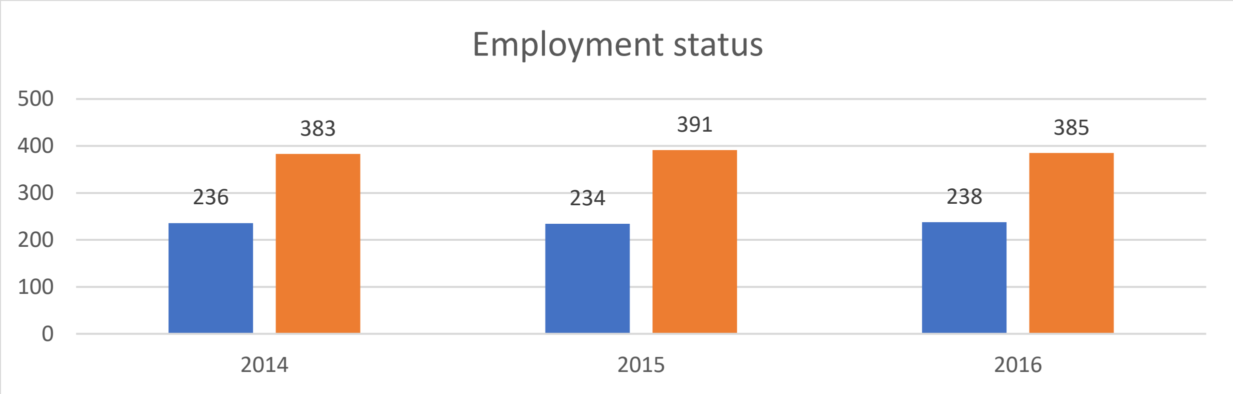


Figure 7 Number of employers and employees in the study. Period 2014-2016, blue is employee, orange is co-owner

Table 8 Mann-whitney test on employment status

	Year	Employment status	N	Mean	SD	Mean rank	P value
DDDAvet poultry	2014	Co-owner	28	17.86	10.48	25.54	0.984
		employee	22	18.20	11.97	25.45	
	2015	Co-owner	29	11.69	7.77	22.69	0.109
		employee	21	14.88	6.69	29.38	
	2016	Co-owner	28	10.28	8.65	25.11	0.830
		employee	22	10.12	7.41	26.00	
DDDAvet veal calves	2014	Co-owner	82	14.21	12.08	53.74	0.656
		employee	26	16.03	14.52	56.88	
	2015	Co-owner	82	13.24	12.91	55.84	0.848
		employee	28	14.46	20.00	54.50	
	2016	Co-owner	80	14.66	16.28	51.80	0.899
		employee	23	15.21	16.82	52.70	
DDDAvet pigs	2014	Co-owner	169	6.05	5.04	111.37	0.713
		employee	51	5.39	3.06	107.63	
	2015	Co-owner	162	5.64	4.87	106.67	0.771
		employee	49	5.57	4.88	103.78	
	2016	Co-owner	158	5.20	3.57	106.27	0.450
		employee	50	4.68	2.78	98.90	
DDDAvet cattle	2014	Co-owner	346	2.33	1.17	274.94	0.160
		employee	189	2.46	2.02	255.29	
	2015	Co-owner	343	2.16	1.10	283.92	**0.045***
		employee	203	2.22	1.55	255.90	
	2016	Co-owner	340	2.38	2.60	282.95	0.162
		employee	210	2.19	1.37	263.44	

Table 9 chi square test on employment status between high and low prescribers.

DDDAvet	Year	Gender	<35 (n)	>65 (n)	Pearson's chi	P value
DDDAvet poultry	2014	Co-owner	11	11	2.004	0.157
		Employee	3	9		
	2015	Co-owner	9	8	1.588	0.208
		Employee	5	11		
	2016	Co-owner	11	12	0.087	0.769
		Employee	6	8		
DDDAvet veal calves	2014	Co-owner	9	19	0.751	0.386
		Employee	6	7		
	2015	Co-owner	15	21	1.007	0.316
		Employee	7	5		
	2016	Co-owner	17	24	0.057	0.812
		Employee	5	6		
DDDAvet pigs	2014	Co-owner	32	44	1.862	0.172
		Employee	16	12		
	2015	Co-owner	38	43	0.379	0.538
		Employee	14	12		
	2016	Co-owner	37	37	0.269	0.604
		Employee	14	11		
DDDAvet cattle	2014	Co-owner	78	102	1.016	0.313
		Employee	61	63		
	2015	Co-owner	73	113	4.837	**0.028***
		Employee	61	56		
	2016	Co-owner	81	115	1.458	0.227
		Employee	63	68		

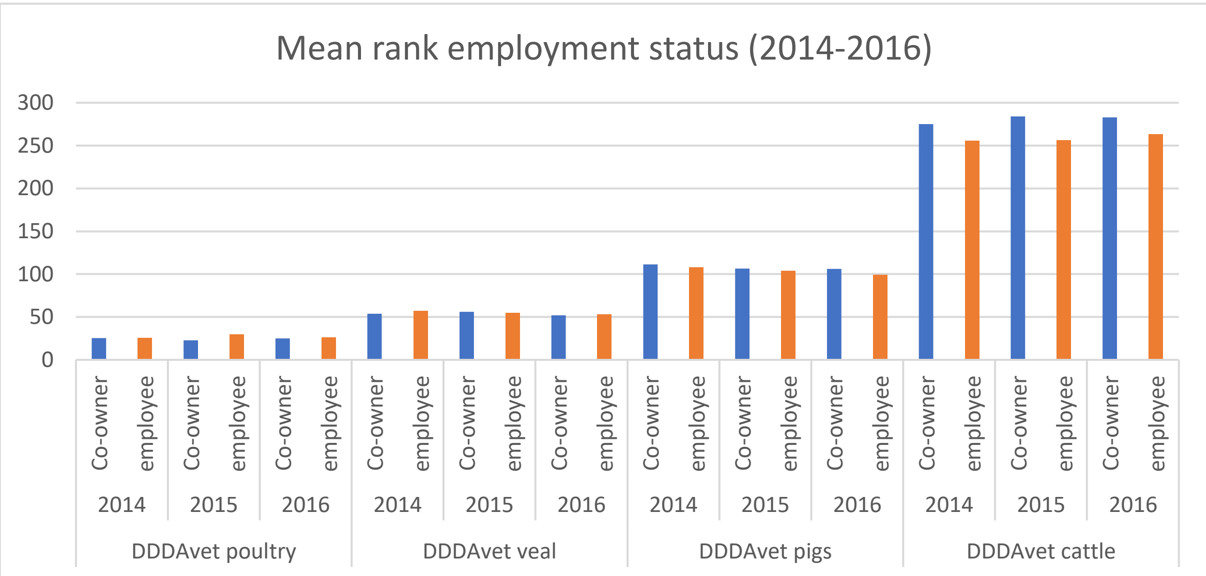


Figure 8 Mean rank in employment status from 2014-2016

Year of graduation

Data of participants in this study showed graduation years from 1955-2016, see figure 9. Linear regression was used to determine if the independent variable 'year of graduation' was associated with the DDDAvet scores in the different livestock species. The regression model showed that there was only a significant variance for poultry in 2016, see table 10.

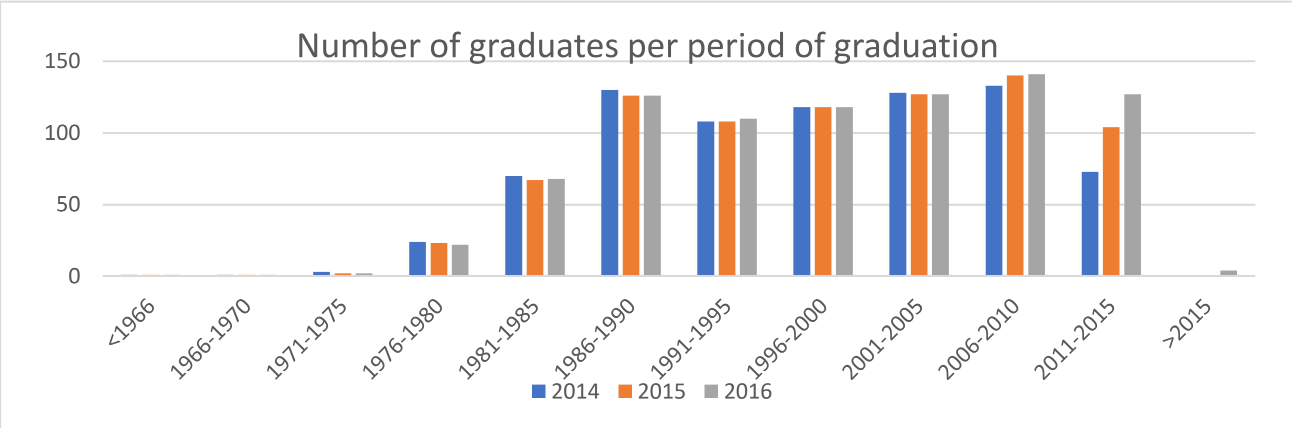
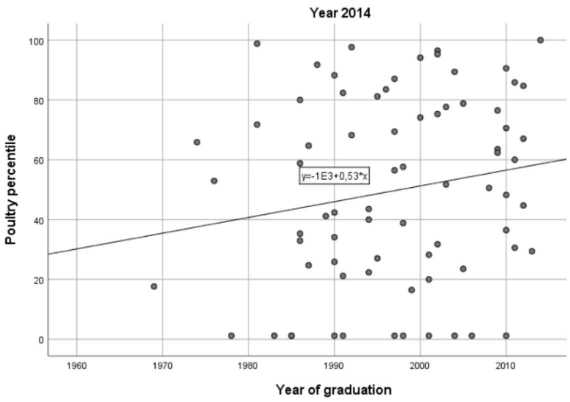
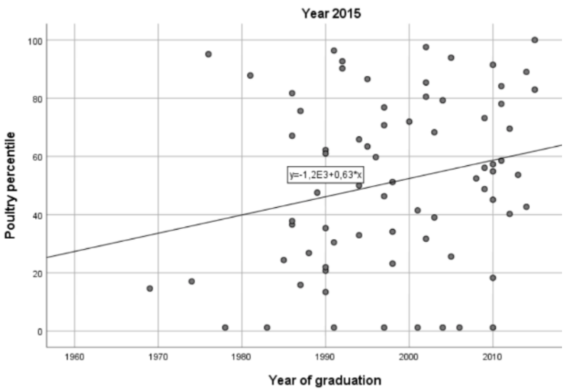


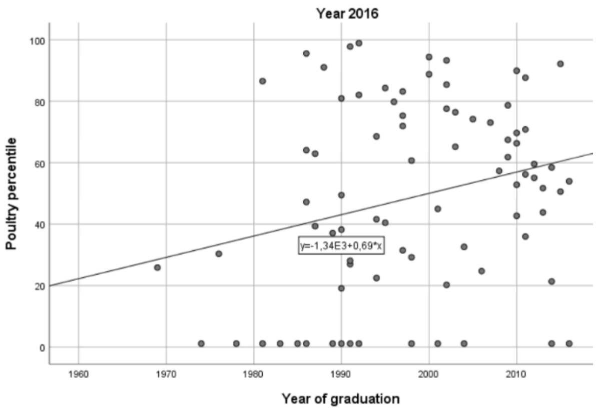
Figure 9 Number of participants per 5 years of graduation. Period 2014-2016

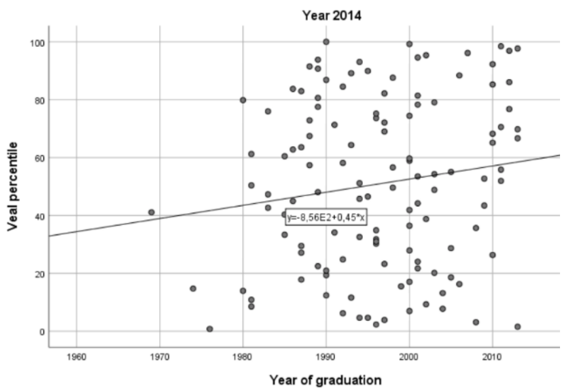
Table 10 linear regression year of graduation

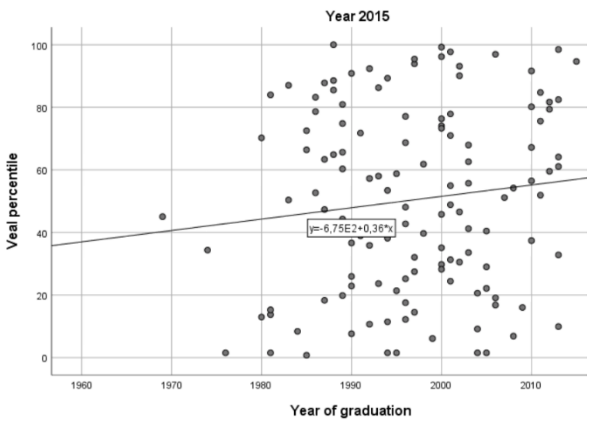
Variabele	Year	R^2	F	B	P value
DDDAvet poultry	2014	0.031	2.348	0.527	0.130
	2015	0.053	3.984	0.627	0.060
	2016	0.064	5.543	0.694	**0.026***
DDDAvet veal calves	2014	0.022	2.746	0.454	0.120
	2015	0.015	1.841	0.363	0.177
	2016	0.010	1.219	0.292	0.272
DDDAvet pigs	2014	0.003	0.803	0.179	0.371
	2015	0.014	3.492	0.360	0.063
	2016	0.015	3.579	0.356	0.080
DDDAvet cattle	2014	0.002	1.204	-0.124	0.273
	2015	0.003	1.795	-0.145	0.115
	2016	0.004	2.386	-0.163	0.123

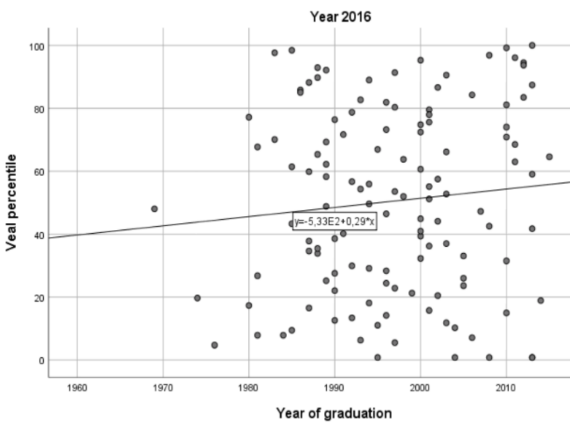

Year 2014
Poultry percentile
y=-1E3+0,53*x
0
20
40
60
80
100
1960
1970
1980
1990
2000
2010
Year of graduation

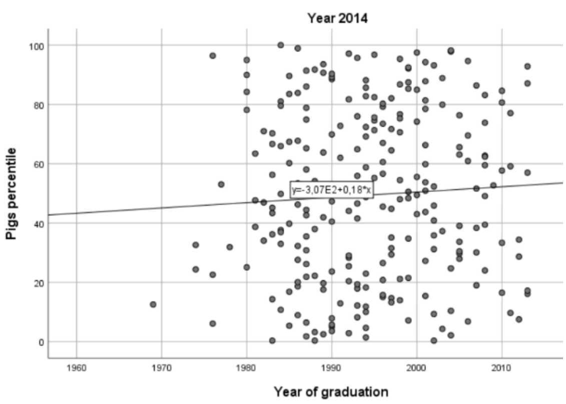

Year 2015
Poultry percentile
y=-1,2E3+0,63*x
0
20
40
60
80
100
1960
1970
1980
1990
2000
2010
Year of graduation

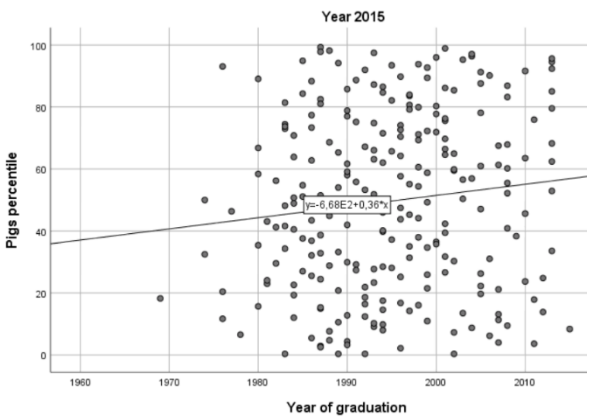

Year 2016
Poultry percentile
y=-1,34E3+0,69*x
0
20
40
60
80
100
1960
1970
1980
1990
2000
2010
Year of graduation


Year 2014
Veal percentile
y=-8,56E2+0,45*x
0
20
40
60
80
100
1960
1970
1980
1990
2000
2010
Year of graduation


Year 2015
Veal percentile
y=-6,75E2+0,36*x
0
20
40
60
80
100
1960
1970
1980
1990
2000
2010
Year of graduation


Year 2016
Veal percentile
y=-5,33E2+0,29*x
0
20
40
60
80
100
1960
1970
1980
1990
2000
2010
Year of graduation


Year 2014
Pigs percentile
y=-3,07E2+0,18*x
0
20
40
60
80
100
1960
1970
1980
1990
2000
2010
Year of graduation


Year 2015
Pigs percentile
y=-6,68E2+0,36*x
0
20
40
60
80
100
1960
1970
1980
1990
2000
2010
Year of graduation

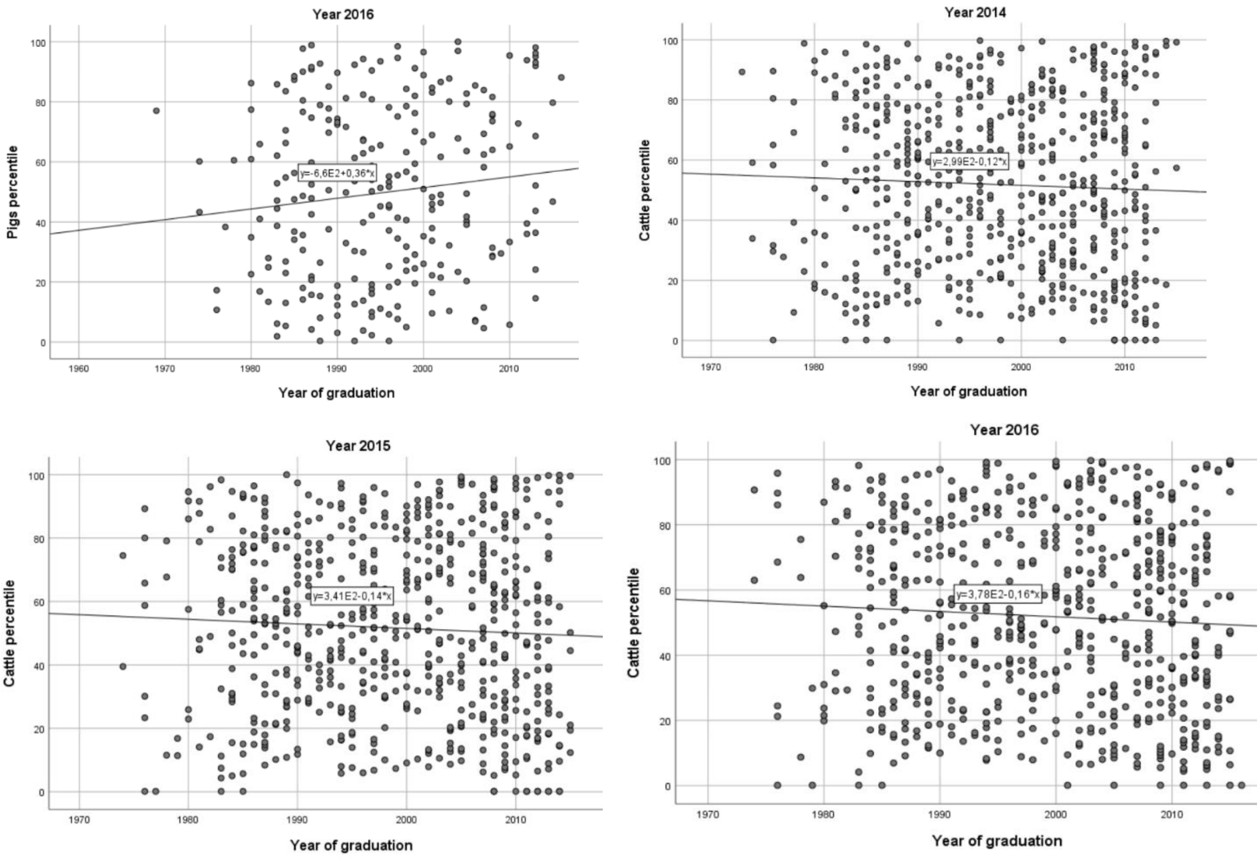


Figure 10 linear regression; year of graduation - DDDAvet in percentiles. Period 2014-2016

Postal code area/practice level

There is a high variance in the number of veterinarians between postal code areas, see figure 11. When the DDDAvet is compared between these areas, a significant difference is found in livestock sectors veal calves and poultry with a kruskall-walace test. DDDAvet cattle shows almost no difference between the areas. For DDDAvet pigs a non-significant difference is seen. See figure 12. When the DDDAvet is compared between colleagues in the same practice, it shows that the level of antibiotic prescription is clustered. The amount of practice influence is also tested and also poultry and veal calves are significantly affected by this factor.

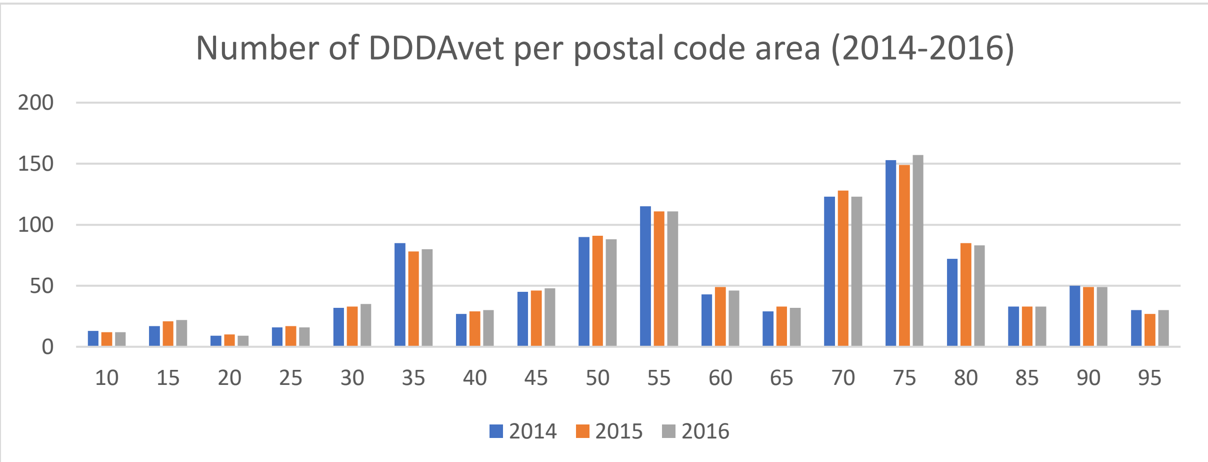
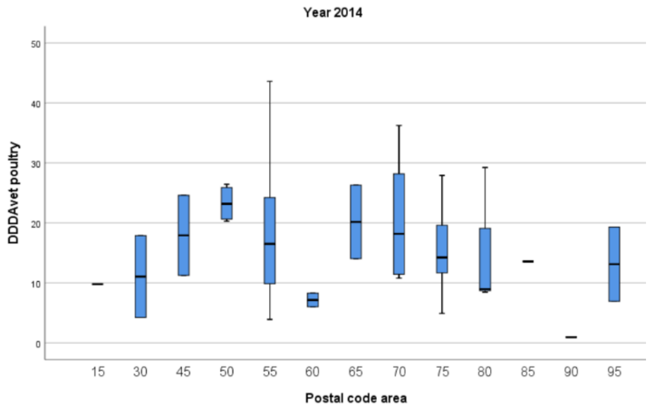
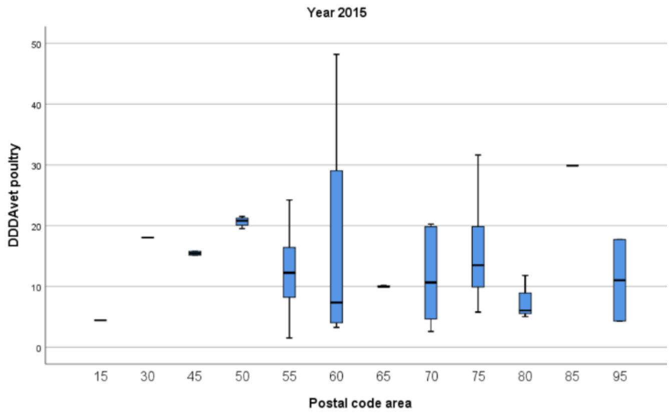
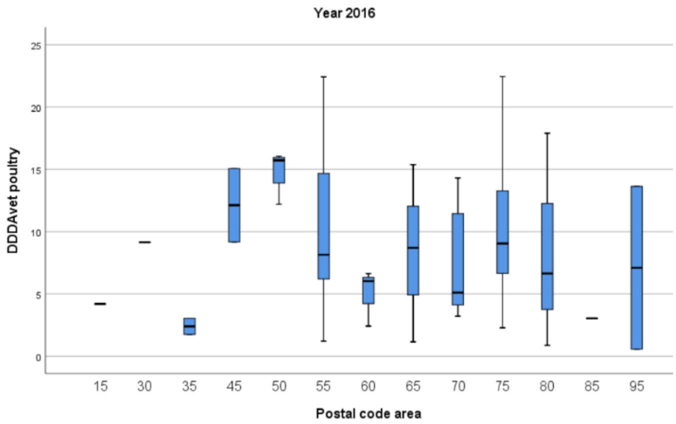
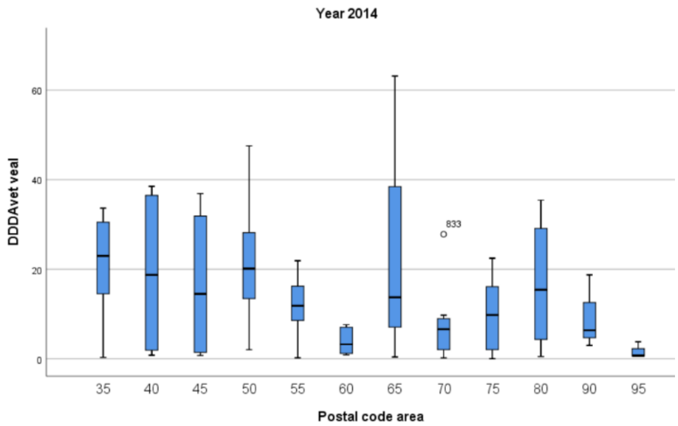


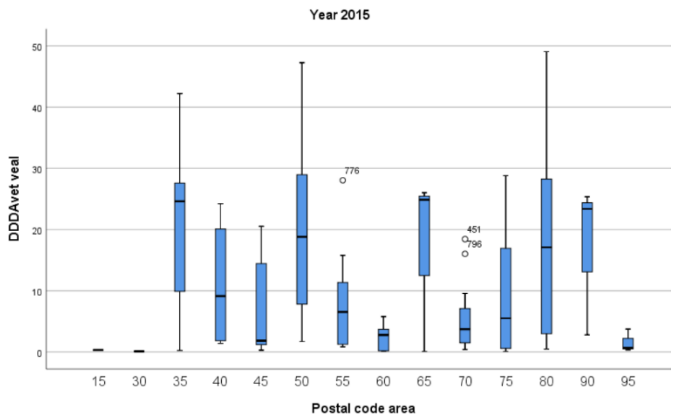
Figure 11 Number of of practitioners in this study per postal code area

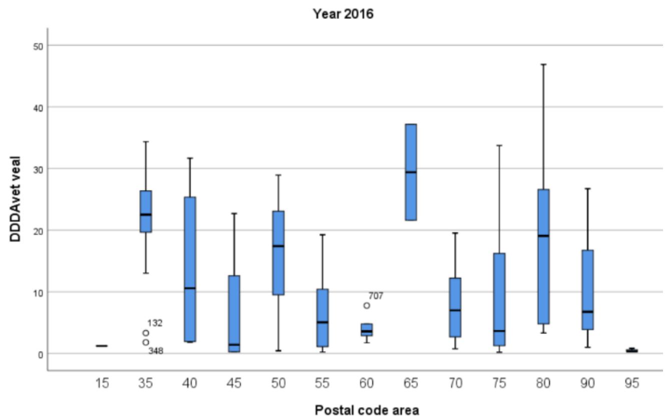

Year 2014
DDDAvet poultry
Postal code area
15 30 45 50 55 60 65 70 75 80 85 90 95

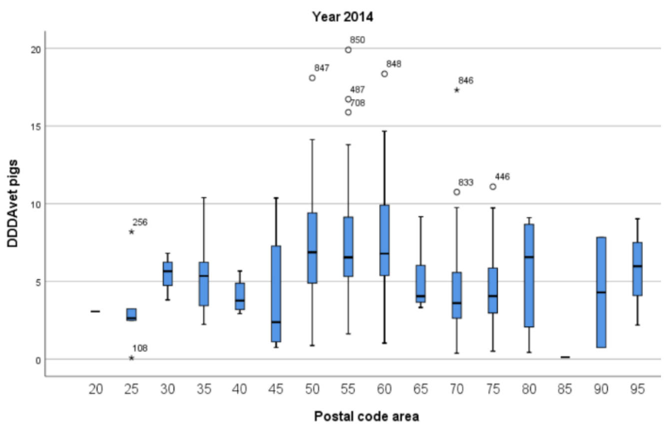

Year 2015
DDDAvet poultry
Postal code area
15 30 45 50 55 60 65 70 75 80 85 95

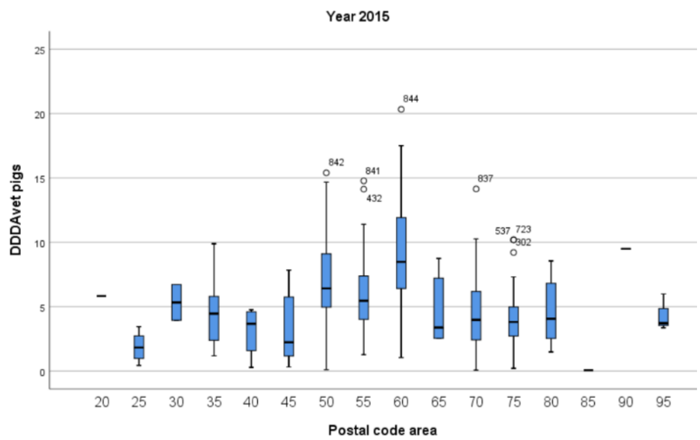

Year 2016
DDDAvet poultry
Postal code area
15 30 35 45 50 55 60 65 70 75 80 85 95


Year 2014
DDDAvet veal
Postal code area
35 40 45 50 55 60 65 70 75 80 90 95


Year 2015
DDDAvet veal
Postal code area
15 30 35 40 45 50 55 60 65 70 75 80 90 95


Year 2016
DDDAvet veal
Postal code area
15 35 40 45 50 55 60 65 70 75 80 90 95


Year 2014
DDDAvet pigs
Postal code area
20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95


Year 2015
DDDAvet pigs
Postal code area
20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

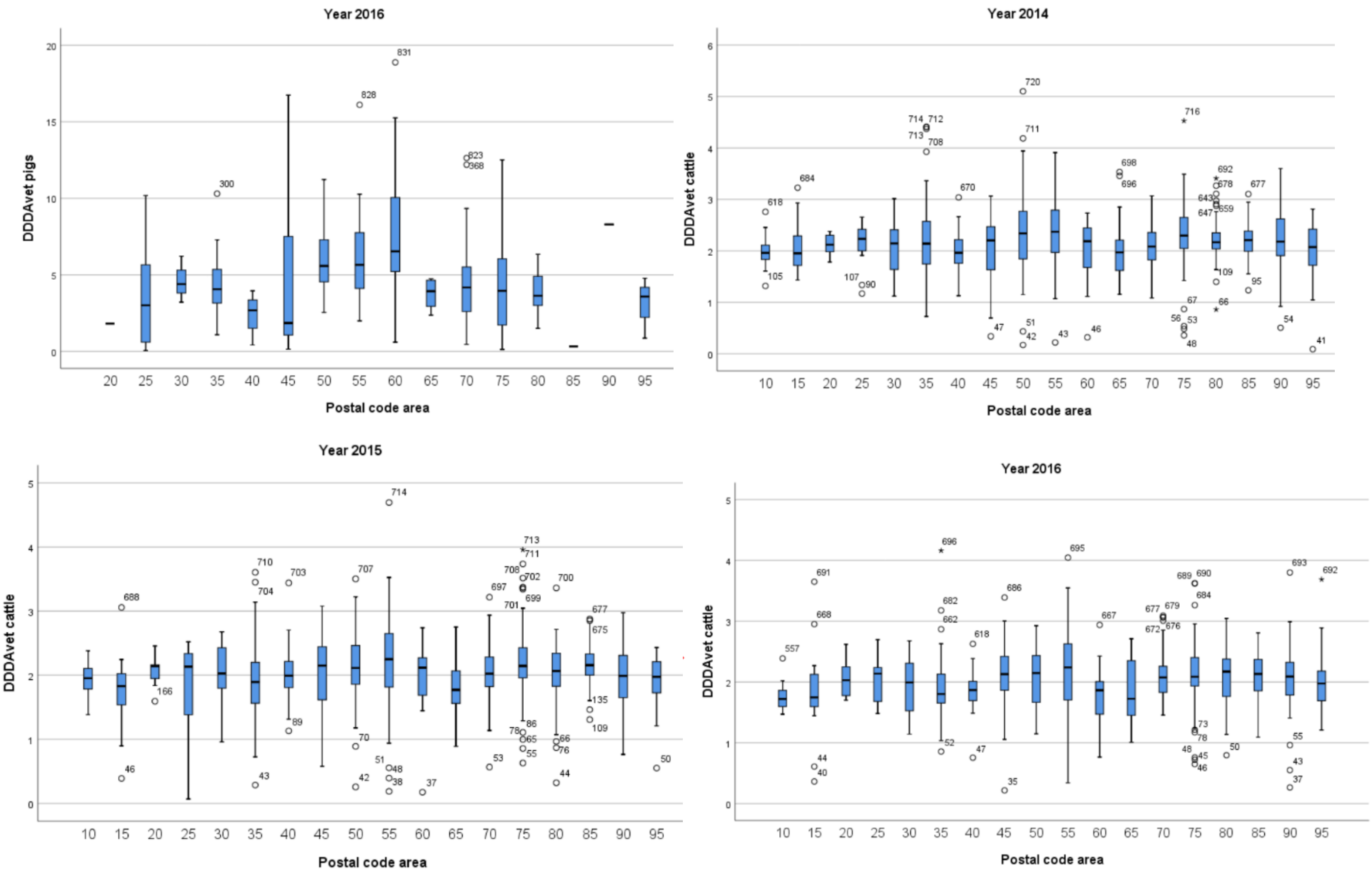


Figure 12 Boxplots DDDAvet per postal code area. Period 2014-2016

DDDAvet between species

When the DDDAvet of one veterinarian was compared between different species, it becomes clear that only the DDDAvet of pigs and veal calves and the DDDAvet of pigs and cattle are positively associated. This means that if a veterinarian is in the high prescription category in pigs, it is also likely that this veterinarian is in the high prescription category for veal calves.

Table 11 Chi square test on correlation between species for individual veterinarians

	Percentile groups DDDAvet poultry	P value	Percentile groups DDDAvet veal calves	P value	Percentile groups DDDAvet pigs	P value
Percentile groups DDDAvet poultry	x	x				
Percentile groups DDDAvet veal calves	1.46 N= 21	0.838	x	x		
Percentile groups DDDAvet Pigs	4.23 N=40	0.381	17.13 N=151	**0.002****	x	x
Percentile groups DDDAvet cattle	9.19 N=55	0.052	3.34 N=309	0.503	15.45 N=475	**0.005****

5.2 Questionnaire

In total 155 veterinarians responded in the questionnaire study. Of the 155 responses, 41 were removed due to double entries, considerable missing data and not working as a veterinarian practitioner. Participants responded from 78 different practices, ranging from 1-6 veterinarians per practice. Other demographic characteristics are represented in table 12. Of the respondents, 46% was a high prescriber and only 19% a low prescriber.

Only the question on the influence of type of practice could be answered due to the low response rate. Division of work in practice, personal division of work and working hours per week had too little variables per individual species to be able to find statistically significant differences with a sufficient power, see figure 13.

Table 12 Demographics of survey

	Subcategories	n
Gender	Male	90
	Female	24
Place of graduation	Utrecht	100
	Ghent	12
Employment status	Employee	41
	Co-owner	71

Table 13 Mann-Whitney test on type of practice

	Year	Type of practice	N	Mean Rank	Significance
DDDAvet poultry	2014	Livestock	2	1.50	0.221
		Mixed	1	3.00	
	2015	Livestock	2	2.00	1.000
		Mixed	1	2.00	
	2016	Livestock	2	2.50	1.000
		Mixed	2	2.50	
DDDAvet veal calves	2014	Livestock	10	13.40	0.958
		Mixed	16	13.56	
	2015	Livestock	11	15.09	0.760
		Mixed	17	14.12	
	2016	Livestock	10	15.30	0.891
		Mixed	19	14.84	
DDDAvet pigs	2014	Livestock	11	22.36	**0.024****
		Mixed	22	14.32	
	2015	Livestock	11	20.91	0.101
		Mixed	22	15.05	
	2016	Livestock	11	23.45	**0.016****
		Mixed	23	14.65	
DDDAvet cattle	2014	Livestock	21	34.14	0.814
		Mixed	48	35.38	
	2015	Livestock	24	34.92	0.557
		Mixed	49	38.02	
	2016	Livestock	25	37.68	0.720
		Mixed	52	39.63	

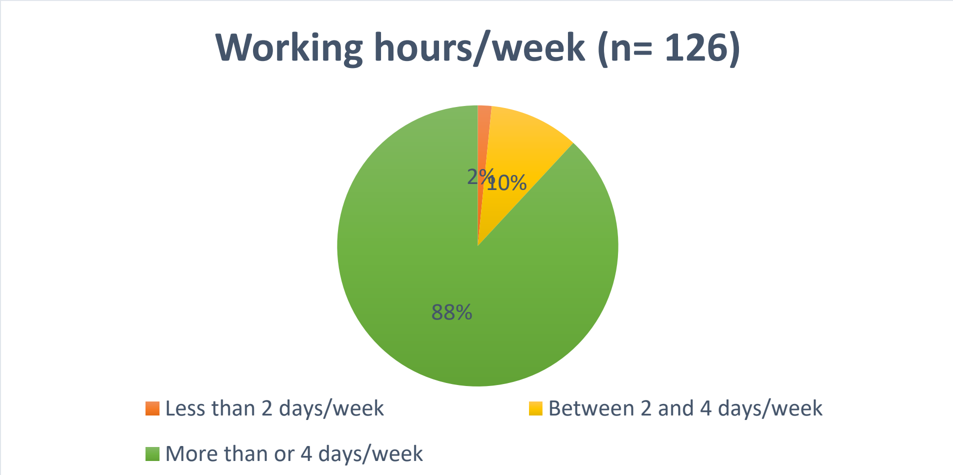


Figure 13 working hours a week of respondents

6. Discussion

The process of antibiotic prescription is complex, which is described in human and veterinary medicine (Hulscher et al, 2010; van Buul et al., 2014; Speksnijder et al., 2015; Coyne et al. 2016). This is one of the first studies to determine the effect of demographic factors on the antimicrobial prescription level of farm animal veterinarians. The difference in prescription behaviour between practices in this study, is in agreement with the study on prescription behaviour in companion animals (Hopman et al, 2019). Also similarities with literature of humane healthcare are found, such as the higher prescription of males in comparison to females. The difference in prescription behaviour is also recognised in humane healthcare (Moghadamnia et al., 2002; Lam & Lam, 2003; Chamany; 2005; Cadieux et al., 2007; Mazzaglia et al., 2003).

The investigated factors did present some significant influences, however these were species specific. Reasons for the identified demographic inequalities between species are not clear. The absolute difference in antimicrobial prescription level between high and low prescribers in cattle was very small which may have influenced the results. With the use of percentiles and the non-parametric tests it is tried to minimize the effect of outliers in the data.

The DDDAvet is based on the prescribed antibiotics on a 1-1 relationship farm. However, other veterinarians in the same practice are able to prescribe antibiotics on this farm too, which may influence the individual factors of the DDDAvet. However, the risk of indicating a false relationship between the demographic factors and the DDDAvet is minimized due to statistics based on 3 years of data. However, some statistical significant associations are not found during the whole period.

The significant difference of prescription behaviour between postal code areas looks related to the amount of intensive farming in the region. Further research is required to see if perhaps the amount and size of farms have an influence on prescription behaviour of a practice. Almost related to postal code area is the difference between practices. Cultural differences between practices may influence individual prescription behaviour.

Limitations

There are some limitations in this study. The data analysis on the large dataset is based on self-reported public data and comes with a risk of human mistakes and not up-to-date data. However, several control steps, such as confirming by a second source, are applied to minimize this bias. Also, the size of the database makes the influence of small mistakes negligible and public data and data from benchmark institutes were gathered earlier than the questionnaire.

The data from the survey relied on practitioners volunteering to answer the questionnaire and was not based on random selection. Of the respondents, 46% was a high prescriber and only 19% a low prescriber which was not representative for the whole population. Other demographic data was representative for the whole population when analysed with a chi square test. The number of number of respondents was very low, which influences the power of the statistical analysis.

7. Conclusion

Appropriate use of antibiotics in animals with clinical needs is required to maintain the efficacy of these antibiotics. Unnecessary use should be limited in order to minimize AMR. Over the last 19 years a reduction in veterinary AMU of 63.8% is accomplished in the Netherlands (SDA, 2018). A further reduction is needed to achieve the 70% reduction target set by the government. In this study the influence of demographic factors on prescription behaviour is analysed to identify prescribing determinants between high and low prescribers. The findings of this study showed some possible implications in demographic factors for understanding the variability in antibiotic prescription in the Netherlands. All significant results are species related which indicates that other key motivators must be present.

Gender seemed to have an effect on prescription levels in cattle, where woman prescribed less then male cattle veterinarians. This difference is visible from 2014 until 2016. Place of graduation shows a significant difference in pigs veterinarians. Alumni from Ghent had higher prescription rates (expressed as DDDAvet pigs) than alumni from Utrecht from 2014-2016. This phenomenon can maybe be explained by the fact that Flemish veterinarians are less supportive in reduction policies, because of the fear of negative consequences in animal health and welfare (Postma et al., 2016). Year of graduation only had a significant effect in 2016. Differences in gender and place of graduation are also found in human healthcare (Moghadamnia et al., 2002; Lam & Lam, 2003; Chamany; 2005; Cadieux et al., 2007; Mazzaglia et al., 2003).

Differences in DDDAvet between co-workers and employees are only seen in 2015 for DDDAvet cattle. The fact that this difference is only visible in 2015 makes it unlikely that this factor has a major influence on prescription behaviour. DDDAvet scores are higher when you are graduated more recently in poultry, veal calves and pigs (not significant except for poultry in 2016). In cattle prescription levels are (not significantly) lower when graduated more recently. These results are not significant except for poultry in 2016. The positive relationships found in humane medicine are not visible in this study on veterinarians. In a study by Speksnijder et al., the optimistic view of young veterinarians on reduction in antibiotic reduction is mentioned and you would have expected a similar outcome in antibiotic use (Speksnijder et al, 2015). However, this is not the case. In human medicine, junior practitioners tend to prescribe antibiotics on recommendation of their senior supervisor. They do this despite the fact that these are not in accordance with current recommendations (de Souza, 2006).

The analysis on postal code area and practice influences shows a difference in use between areas/practices for poultry and veal calves DDDAvet. The prescription behaviour in these livestock sectors are influenced by colleagues. When after that the correlation between different sectors and prescription behaviour from individual veterinarians is checked, you see a clustering in cattle-pig and pig-veal calves prescription behaviour. The influence of type of practice is only visible in DDDAvet pig 2014 and 2016 where livestock practices prescribed more than mixed practices with companion animals. Conclusions are summarized in table 14

Table 14 Summarized conclusions

Significant difference	Poultry	Veal calves	Pigs	Cattle
Gender	No	No	No	Yes (+)
Place of graduation	No	No	Yes (+)	No
Year of graduation	Yes - 2016	No	No	No
Employment status	No	No	No	Yes - 2015
Postal code area	Yes	Yes	No	No
Influence of practice	Yes	Yes	No	No
Correlation prescription groups with other species	No	Yes	Yes	Yes
Type of practice	No	No	Yes – 2014 & 2016	No

Recommendations

- Factors which influenced the DDDAvet are species specific so interventional strategies should also be performed species specific.
- The influence of the practice where the veterinarians work, has an impact on prescription behaviour. Especially for intensive livestock farming. A DDDAdap would maybe encourage a whole team to implement prudent antibiotic use.
- Further investigation is needed to answer the question why alumni from Ghent have higher prescription levels in DDDAvet pigs than alumni from Utrecht. Are they located in the same area or is it possible that if more alumni from Ghent work together, it influences practise decisions.
- Further investigation is needed to explain the difference between postal code areas and practices. There may be an influence in the amount of veterinarians who work at a practice and prescription behaviour or a cultural difference between practices.
- Individual attitudes towards antibiotic prescription should be analysed.
- Further research is required on the influence of the size and number of farms in the customer base of a practise on prescription behaviour.

8. References

Akkerman, A., Kuyvenhoven, M., van der Wouden, Johannes C, Verheij, T. J. M., & Verheij, T. (2005). Prescribing antibiotics for respiratory tract infections by GPs: Management and prescriber characteristics. *British Journal of General Practice, 55*(511), 114-118.

Alanis, A. J. (2005). Resistance to antibiotics: Are we in the post-antibiotic era? *Archives of Medical Research, 36*(6), 697. doi:10.1016/j.arcmed.2005.06.009

Barton, M. D. (2000). Antibiotic use in animal feed and its impact on human health. *Nutrition Research Reviews, 13*(2), 279-299. doi:10.1079/095442200108729106

Besser, R. E. (2005). Knowledge attitudes and reported practices among obstetrician gynaecologists in the USA regarding antibiotic prescribing for upper respiratory tract infections. doi:10.1155%2F2005%2F405868

Bharathiraja, R. (2005). Factors affecting antibiotic prescribing pattern in pediatric practice. *The Indian Journal of Pediatrics, 72*(10), 877. doi:10.1007/BF02731121

van Buul, L. W., van der Steen, J. T., Doncker, S. M., Achterberg, W. P., Schellevis, F. G., Veenhuizen, R. B., & Hertogh, C. M. (2014). Factors influencing antibiotic prescribing in long-term care facilities: a qualitative in-depth study. *BMC geriatrics*, *14*(1), 136.

Cadieux, G., Tamblyn, R., Dauphinee, D., & Libman, M. (2007). Predictors of inappropriate antibiotic prescribing among primary care physicians. *CMAJ: Canadian Medical Association Journal, 177*(8), 877-883. doi:10.1503/cmaj.070151

Carr, N. F., Wales, S. G., & Young, D. (1994). Reported management of patients with sore throat in Australian general practice. *British Journal of General Practice, 44*(388), 515-518.

Cho, H. J., & Kim, C. B. (2002). Prescription behaviours of office-based doctors to standardized common cold patients in Korea. *Pharmacoepidemiology and Drug Safety, 11*(5), 401-405. doi:10.1002/pds.718

Cogliani C., Goossens H. and Greko C., 2011. Restricting Antimicrobial Use in Food Animals: Lessons from Europe. *Microbe, 6(6)*, pp. 274-278.

Cosgrove, S. (2006). The relationship between antimicrobial resistance and patient outcomes: Mortality, length of hospital stay, and health care costs. *Clinical Infectious Diseases, 42 Suppl 2*(2_supplement), S82-S89. doi:10.1086/499406

Cotter, M. (2007). Antibiotic prescription practices of general practitioners. *Irish Medical Journal, 100*(9), 598.

Dean, W.R., Mcintosh, W.A., Scott, H.M. and Barling, K.S., 2011. The Role of Trust and Moral Obligation in Beef Cattle Feed-lot Veterinarians' ContinGhent Adoption of Antibiotic Metaphylaxis Recommendations*. Int Jrnl of Soc of Agr & Food,* 18(2), pp. 104-120.

De Briyne, N., Atkinson, J., Pokludová, L., Borriello, S. P., & Price, S. (2013). Factors influencing antibiotic prescribing habits and use of sensitivity testing amongst veterinarians in Europe. *Veterinary Record, 173*(19), 475-475. doi:10.1136/vr.101454

De Souza, V., MacFarlane, A., Murphy, A., Hanahoe, B., Barber, A., & Cormican, M. (2006). A qualitative study of factors influencing antimicrobial prescribing by non-consultant hospital doctors. *Journal of Antimicrobial Chemotherapy, 58*(4), 840-843. doi:10.1093/jac/dkl323

De Sutter, A. I., De Meyere, M. J., De Maeseneer, J. M., & Peersman, W. P. (2001). Antibiotic prescribing in acute infections of the nose or sinuses: A matter of personal habit? *Family Practice, 18*(2), 209-213. doi:10.1093/fampra/18.2.209

Derks, M., van de Ven, Lindsay M A, van Werven, T., Kremer, W. D. J., & Hogeveen, H. (2012). The perception of veterinary herd health management by Dutch dairy farmers and its current status in the Netherlands: A survey. *Preventive Veterinary Medicine, 104*(3-4), 207-215. doi:10.1016/j.prevetmed.2011.12.019

Dodds, D. R. (2017). *Antibiotic resistance: A current epilogue* doi: https://doi.org/10.1016/j.bcp.2016.12.005

Fakih, M., Hilu, R., Savoy Moore, R., & Saravolatz, L. (2003). Do resident physicians use antibiotics appropriately in treating upper respiratory infections? A survey of 11 programs. *Clinical Infectious Diseases, 37*(6), 853-856. doi:10.1086/377503

Fernández Liz, E., Modamio, P., Catalán, A., Lastra, C., Rodríguez, T., Mariño, E., et al. (2008). Identifying how age and gender influence prescription drug use in a primary health care environment in Catalonia, Spain. *British Journal of Clinical Pharmacology, 65*(3), 407-417. doi:10.1111/j.1365-2125.2007.03029.x

Finkelstein, J., Stille, C., Rifas Shiman, S., & Goldmann, D. (2005). Watchful waiting for acute otitis media: Are parents and physicians ready? *Pediatrics, 115*(6), 1466-1473. doi:10.1542/peds.2004-1473

Fleming, A. (1929). On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of b. influenzae. *British Journal of Experimental Pathology, 10*(3), 226-236.

Grave, K., Torren Edo, J., & Mackay, D. (2010). Comparison of the sales of veterinary antibacterial aGhents between 10 European countries. *Journal of Antimicrobial Chemotherapy, 65*(9), 2037-2040. doi:10.1093/jac/dkq247

Hopman, N.E.M, van Dijk, Marloes A.M., Broens, E.M., Wagenaar, J.A., Heederik, D.J.J & van Geijlswijk, I.M. (2019). Quantifying Antimicrobial Use in Dutch Companion Animals. *Frontiers in Veterinary Science*, 6, (pp. 158)

Huang, N. (2005). Antibiotic prescribing by ambulatory care physicians for adults with nasopharyngitis, URIs, and acute bronchitis in Taiwan: A multi-level modeling approach. *Family Practice, 22*(2), 160. doi:10.1093/fampra/cmh734

Hulscher, M. E., van der Meer, J. W., & Grol, R. P. (2010). Antibiotic use: how to improve it?. *International Journal of Medical Microbiology*, 300(6), 351-356.

Hummers-Pradier, E. (2005). Influence of patient symptoms and physical findings on general practitioners treatment of respiratory tract infections a direct observation study. *BMC Family Practice, 6*, 6. doi:10.1186%2F1471-2296-6-6

Komolafe, O. O. (2003). Antibiotic resistance in bacteria-an emerging public health problem. *Malawi Medical Journal, 15*(2), 63. doi:10.4314/mmj.v15i2.10780

Lam, T. P., & Lam, K. F. (2003). Why do family doctors prescribe antibiotics for upper respiratory tract infection? *International Journal of Clinical Practice, 57*(3), 167-169.

Leverstein-van Hall, M. A., Dierikx, C. M., Cohen Stuart, J., Voets, G. M., van den Munckhof, M P, van Essen-Zandbergen, A., et al. (2011). Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. *Clinical Microbiology and Infection, 17*(6), 873-880. doi:10.1111/j.1469-0691.2011.03497.x

Lin, P. L., Oram, R. J., Lauderdale, D. S., Dean, R., & Daum, R. S. (2000). Knowledge of centers for disease control and prevention guidelines for the use of vancomycin at a large tertiary care children's hospital. *The Journal of Pediatrics, 137*(5), 694-700. doi:10.1067/mpd.2000.109113

Mayer, S., Österle, A., & Oesterle, A. (2015). Socioeconomic determinants of prescribed and non-prescribed medicine consumption in Austria. *European Journal of Public Health, 25*(4), 597-603. doi:10.1093/eurpub/cku179

Pradier, C., Rotily, M., Cavailler, P., Haas, H., Pesce, A., Dellamonica, P., et al. (1999). Factors related to the prescription of antibiotics for young children with viral pharyngitis by general practitioners and paediatricians in south-eastern France. *European Journal of Clinical Microbiology & Infectious Diseases, 18*(7), 510-514. doi:10.1007/s100960050334

Postma, M., Speksnijder, D. C., Jaarsma, D. A. C., Verheij, T. J., Wagenaar, J. A., & Dewulf, J. (2016). Opinions of veterinarians on antimicrobial use in farm animals in Flanders and the Netherlands. *Veterinary record*, vetrec-2015.

Quinn, P. J., Markey, B. K., Leonard, F. C., Hartigan, P., Fanning, S., & FitzPatrick, E. S. (2011). *Veterinary microbiology and microbial disease.* (2nd ed. ed.). Hoboken: John Wiley & Sons. Retrieved from https://utrechtuniversity.on.worldcat.org/oclc/778339100

Stichting Diergeneesmiddelen Autoriteit. (2015) Usage of antibiotics in agricultural livestock in the Netherlands in 2014. Trends and benchmarking of livestock farms and veterinarians. Accessed Mar. 22, 2018. Retrieved from https://www.autoriteitdiergeneesmiddelen.nl/en/publications/general-reports

Stichting Diergeneesmiddelen Autoriteit. (2018) Usage of antibiotics in agricultural livestock in the Netherlands in 2017. Trends and benchmarking of livestock farms and veterinarians. Accessed Mar. 22, 2018. Retrieved from https://www.autoriteitdiergeneesmiddelen.nl/en/publications/general-reports

Stichting Diergeneesmiddelen Autoriteit. (2019) SDa-rapport 'antibioticumgebruik in 2018 Accessed Mar. 22, 2018. Retrieved from https://www.autoriteitdiergeneesmiddelen.nl/en/publications/general-reports

Speksnijder, D. C., Jaarsma, A. D. C., Van Der Gugten, A. C., Verheij, T. J., & Wagenaar, J. A. (2015a). Determinants associated with veterinary antimicrobial prescribing in farm animals in the Netherlands: a qualitative study. *Zoonoses and public health*, *62*, 39-51.

Speksnijder, D. C., Mevius, D. J., Bruschke, C. J. M., & Wagenaar, J. A. (2015b). Reduction of veterinary antimicrobial use in the Netherlands. the Dutch success model. *Zoonoses and Public Health, 62 Suppl 1*, 79-87. doi:10.1111/zph.12167

Stokstad, E. (1950). Further observations on the animal protein factor. *Proceedings of the Society for Experimental Biology and Medicine, 73*(3), 523-528.

Strebhardt, K., & Ullrich, A. (2008). z *Nature Reviews.Cancer, 8*(6), 473-480. doi:10.1038/nrc2394

Swann MM et al. Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine. London: Her Majesty's Stationery Office, 1969.

Teng, C. L., Achike, F. I., Phua, K. L., Norhayati, Y., Nurjahan, M. I., Nor, A. H., et al. (2004). General and URTI-specific antibiotic prescription rates in a Malaysian primary care setting. *International Journal of Antimicrobial AGhents, 24*(5), 496-501. doi:10.1016/j.ijantimicag.2004.06.015

Thorpe, J., Smith, S., & Trygstad, T. (2004). Trends in emergency department antibiotic prescribing for acute respiratory tract infections. *Annals of Pharmacotherapy, 38*(6), 928-935. doi:10.1345/aph.1D380

Tomayko, J. F. (2014). The challenge of antimicrobial resistance: New regulatory tools to support product development. *Clinical Pharmacology & Therapeutics, 96*(2), 166-168.

van den Bogaard, A E, & Stobberingh, E. E. (1999). Antibiotic usage in animals: Impact on bacterial resistance and public health. *Drugs, 58*(4), 589-607. doi:10.2165/00003495-199958040-00002

van der Velden, K. (1993). Prescription of antibiotics and prescribers characteristics. A study into prescription of antibiotics in upper respiratory tract infections in general practice. *Family Practice, 10*, 366-370. doi:10.109FfampraF10.4.366

Voss, A., Loeffen, F., Bakker, J., Klaassen, C., & Wulf, M. (2005). Methicillin-resistant staphylococcus aureus in pig farming. *Emerging Infectious Diseases, 11*(12), 1965-1966. doi:10.3201/eid1112.050428

Watson, R. L., Dowell, S. F., Jayaraman, M., Keyserling, H., Kolczak, M., & Schwartz, B. (1999). Antimicrobial use for paediatric upper respiratory infections: Reported practice, actual practice, and parent beliefs. *Pediatrics, 104*(6), 1251-1257. doi:10.1542/peds.104.6.1251

Wierup, M. (2001). The Swedish experience of the 1986 year ban of antimicrobial growth promoters, with special reference to animal health, disease prevention, productivity, and usage of antibiotics. *Microbial Drug Resistance, 7*(2), 183-190. doi:10.1089/10766290152045066