



PhD thesis 2016

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Applications of VetStat data on pig antimicrobial usage

Opportunities, challenges and restrictive legislation



PhD thesis 2016 ▪ Nana Dupont

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Preface

Time changes all things. This has been especially true for my PhD project, which has centered on highly contemporary topics. When I initially embarked on my journey as a PhD student, the Danish Veterinary Medicines Statistics Program (VetStat) had already been in place for slightly more than a decade. At the time, VetStat data were only available to a select few whose access was contingent upon both a screening process and security clearance. Hence, a primary aim of my original PhD plan was to describe the VetStat database.

In late 2011, it was decided that VetStat data should be available to the public in general. This emphasized the need to describe the challenges encountered while working with VetStat data in order to mitigate the risk of erroneous conclusions. In addition to the increased database access, Denmark had previously introduced unique legislation in December 2010 penalizing pig herds with a high metaphylactic and therapeutical antimicrobial use. The following rapid decline in national antimicrobial usage represented a unique opportunity to investigate whether a decrease in antimicrobial consumption prompted by legislation had affected productivity and health.

In 2011, I became enrolled as a 4+4 PhD, adding one year to the usual allotted time for a PhD project. Consequently, the first two years of my PhD were spent as a combined Master and PhD student, during which time I was both enrolled in the mandatory veterinary Master's courses and writing my Master's thesis while concurrently working on my PhD. Following completion of my Master's thesis, I was then solely enrolled as a PhD student. The 4+4 PhD has granted me a major opportunity to focus my Master's thesis on the subject of my PhD. To a large extent, the Background chapter of this PhD thesis builds upon knowledge obtained through the extensive literature review of my Master's thesis. Naturally, more knowledge has been attained since, as new papers have been published and the attendance at meetings and conferences has expanded my understanding. However, it was the process of writing my Master's thesis that created the knowledge foundation for this PhD thesis.

During my PhD I have been enrolled at the Production and Health unit, Department of Large Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen. The PhD project was financed by the Danish Pig Levy Fund and the University of Copenhagen. Additional funding was generously provided by the Danish Centre for Animal Welfare. The project work was carried out 2011 to 2016.

The results of this PhD thesis are relevant to both (i) researchers, who work with VetStat data on antimicrobial usage or in other respects have an interest in obtaining a deeper understand-

ing of antimicrobial sales data in a large national database; and (ii) stakeholders with an interest in productivity and health consequences following implementation of punitive antimicrobial restrictive legislation.

Acknowledgements

My PhD has in truth been a journey, both in time and knowledge. Along the way I have had the privilege to meet some truly amazing and inspiring people.

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A great thanks goes out to all the participating farmers and veterinarians without whom a great part of my PhD would not have been possible.

I would also like to acknowledge all the extremely skilled people, whom I have had the immense privilege to work with during the five years of my PhD enrollment, including – but definitely not limited to - my current and previous colleagues at IPH, the VetStat researcher group and everyone at Axelborg who all made me feel incredibly welcome. Thank you for making this journey truly memorable and filled with wonderful experiences. A special thought goes out to Mette Fertner, who has been my partner in crime since her own PhD project started back in 2011. Mette – you have truly been the best colleague anyone could wish for.

Also a big thanks to my friends and family, who patiently hung around, even though I never had time to meet - I promise to bake a cake sometime soon.

I would like to dedicate this PhD thesis to Ulle, Rand and Christian, for always believing and being the most insanely inspiring persons in the world anyone could hope to have in their life.

Scientific work

List of papers included in the thesis

- I. Nana Dupont, Mette Fertner, Anna Camilla Birkegård, Vibe Dalhoff Andersen, Gitte Blach Nielsen, Amanda Brinch Kruse, Leonardo de Knecht (2016)
Improving institutional memory on challenges and methods for estimation of pig herd antimicrobial exposure based on data from the Danish Veterinary Medicines Statistics Program (VetStat).
Manuscript submitted to Preventive Veterinary Medicine March 2016.
- II. Nana Dupont, Mette Fertner, Charlotte Sonne Kristensen, Nils Toft, Helle Stege (2016)
Reporting the national Danish pig antimicrobial consumption: Influence of assigned daily dosage values and population measurement.
Manuscript accepted in Acta Veterinaria Scandinavica April 2016.
- III. Nana Dupont, Mette Fertner, Charlotte Sonne Kristensen, Helle Stege (2016)
Changes in productivity and health in Danish weaners and finishers following introduction of the "yellow card" antimicrobial legislation.
Manuscript submitted to Preventive Veterinary Medicine March 2016.

Additional scientific work

Not included in the thesis except for a revised excerpt of publication B. Shown in chronological order

- A. Nana Dupont, Helle Stege, Nils Toft, Margit Andreasen, Claes Enøe (2012)
Reporting antibiotic consumption for Danish pigs – effect of the denominator.
In: Proceedings of the 22nd International Pig Veterinary Society (IPVS) Congress (1), 216. Presented at the 22nd IPVS Congress 2012, Jeju, South Korea. Winner of the Travel Award.
Abstract and oral presentation (peer reviewed).
- B. Nana Dupont, Helle Stege (2013)

Vetstat – Monitoring usage of antimicrobials in animals.

In: Challenges and benefits of health data recording in the context of food chain quality, management and breeding: Proceedings of the ICAR Conference (17), 21-35. Presented at the ICAR Conference 2013, Århus, Denmark.

Conference paper and oral presentation (peer reviewed).

- C. Tine Rousing, Jan Tind Sørensen, Nana Dupont (2014)

Does antimicrobial treatment level explain animal welfare in pig herds?

Presented at the 6th International Conference on the Assessment of Animal Welfare at Farm and Group Level (WAFL) 2014, Clermont-Ferrand, France.

Abstract and poster (peer reviewed).

- D. Nana Dupont, Mette Fertner, Helle Stege (2014)

Welfare (productivity) consequences of the Danish “Yellow Card” debate.

In: Proceedings of the 23rd International Pig Veterinary Society (IPVS) Congress (1), 128. Presented at the 23rd IPVS Congress 2014, Cancun, Mexico.

Abstract and oral presentation (peer reviewed).

- E. Nana Dupont, Helle Stege (2014)

Welfare (findings at slaughter) consequences following a reduction in antibiotic use.

Presented at the 3rd international Conference on Responsible Use of Antibiotics in Animals 2014, Amsterdam, the Netherlands.

Abstract and poster (peer reviewed).

- F. Mette Fertner, Nana Dupont, Anette Boklund, Helle Stege, Nils Toft (2014)

Success factors in weaner production – with limited antimicrobials, high health and productivity. Case studies from Denmark.

Presented at the 29th NKVet Symposium on Responsible use of antibiotics in animal practice 2014, Copenhagen, Denmark.

Abstract and poster (peer reviewed).

- G. Nana Dupont, Mette Fertner, Ken Steen Pedersen, Nils Toft, Helle Stege (2014)

Rapportering af danske svins antibiotikaforbrug – hvor stor betydning har beregningsmetoden?

Dansk Veterinær Tidsskrift 97 (14), 33-38.

Scientific paper.

- H. Mette Fertner, Anette Boklund, Nana Dupont, Claes Enøe, Helle Stege, Nils Toft (2015)

Weaner production with low antimicrobial usage: a descriptive study.

Acta Veterinaria Scandinavica 57 (38). doi: 10.1186/s13028-015-0130-2

Scientific paper.

- I. Mette Fertner, Javier Sanchez, Anette Boklund, Henrik Stryhn, Nana Dupont, Nils Toft (2015)

Persistent Spatial Clusters of prescribed Antimicrobials among Danish Pig Farms – A Register-Based Study.

PLoS ONE 10 (8), e0136834. doi: <http://dx.doi.org/10.1371/journal.pone.0136834>

Scientific paper.

Summary

The two overall purposes of the PhD were (i) to aid the understanding of VetStat data on pig antimicrobial consumption in relation to scientific research on usage patterns and effects of standardized calculations; and (ii) to investigate if the rapid decrease in antimicrobial consumption following the introduction of the yellow card initiative had affected pig health and productivity. The aims were covered in three separate studies.

Study 1

The first study focused on describing the present structure of VetStat through interviews, a literature- and a database study. Two key publications were identified and eight persons interviewed. Overall, the validity and completeness of VetStat data have increased substantially since its implementation in 2000. Antimicrobials sold for use in pigs are primarily registered by the pharmacies. However, despite a high degree of validity within pharmacy registrations on quantity and type, errors, such as e.g. erroneous age group, still occur in a small percentage of entries on pig antimicrobial sales.

Study 2

The second study (paper I + paper II) focused on delineating selected major challenges encountered when using VetStat data to estimate national and herd level pig antimicrobial consumption.

Paper I focused on describing a select set of challenges encountered when attempting to estimate actual herd antimicrobial consumption and propose corresponding solutions. These were chosen and formulated through discussion meetings in an inter-institutional group consisting of five PhD students and one Assistant Professor, all of whom were performing research based on VetStat data. The identified challenges could be divided into two main categories: (i) challenges arising due to data quality and system structure; and (ii) challenges arising during actual calculation of antimicrobial usage and data handling. Essentially, all major challenges could be attributed to the difficulties encountered when attempting to transform secondary sales data into an estimation of true exposure. The importance of each challenge was found to be highly contingent on the pertinent research question.

Paper II focused on investigating to which degree assigned Animal Daily Dose (ADD) values and population measurement influenced the calculated national pig antimicrobial consumption with a specific emphasis on trend over time. The study was performed solely as a retrospective observational database study investigating antimicrobial consumption from 2007 to

2013, calculated as ADDs per pig per year based on (i) three different sets of values for dosage per kg live weight (ADD-values) utilized by major Danish institutions and (ii) four measurements for the Danish pig population. Calculated results and trends were presented using descriptive statistics. Over time, results were found to vary greatly depending on both chosen set of ADD-values and population measurement. From 2007 to 2013, change in ADDs/pig/year was found to vary between an 11% decrease and a 22% depending on calculation method.

Study 3

The third study (paper III) was performed as a retrospective observational study and investigated (i) how the reduction in antimicrobial consumption had been achieved according to veterinarians and farmers; and (ii) whether the rapid decrease in antimicrobial consumption following introduction of the yellow card initiative had affected pig productivity and health, measured as mortality, daily weight gain, lean meat percent and lesions at slaughter. In total, 202 herds and 58 veterinarians replied to the questionnaire on how the antimicrobial reduction had been achieved. The most prevalent answers were an increased use of vaccines, less herd medication and staff education. Overall, both herds with a high- and herds with a low antimicrobial consumption prior to the introduction of the yellow card initiative were found to have decreased their antimicrobial consumption. For weaners, mortality was found to have increased significantly (49 herds; 2.4% to 3.0%; $p=0.0001$); and a lower average daily weight gain (43 herds; 447 to 436 grams/day; $p=0.12$) with higher standard deviation (43.2 to 48.1; $p=0.56$) was also observed. For finishers, trends were observed towards a higher mortality (3.3% to 3.7%; $p=0.51$), lower average daily weight gain (890 to 867 grams per day; $p=0.71$) and higher daily weight gain standard deviation (58.8 to 64.0; $p=0.43$). Abattoir data were obtained for 75 herds. Lean meat percent had increased significantly (60.05 to 60.18; $p<0.0001$) but no change was seen in the standard deviation. The prevalences of 13 types of lesions at slaughter were investigated before and after the introduction of the yellow card initiative using a multilevel model (pig, batch and herd) with a binomial outcome. Significant increases in localized tail bites (OR= 1.8), chronic peritonitis (OR= 1.3) and abscesses in heads and ears (OR= 1.2) were observed ($p<0.0001$). Chronic pleuritis (OR= 0.9), abscesses in front- mid- and rear section (PR= 0.84), chronic pneumonia (OR= 0.8), abscesses in feet and legs (OR= 0.7) and infected tail bites (OR= 0.4) all decreased significantly ($p<0.0001$). The prevalence of osteomyelitis, chronic enteritis and chronic infectious arthritis did not change significantly.

Conclusions

VetStat data present a rare opportunity to closely monitor pig antimicrobial usage at both national and herd level. However, when interpreting VetStat data it is essential to keep in mind that VetStat data reflect sales and not actual usage patterns; and that errors still may occur at all levels. Therefore the responsibility rests with the individual researcher to take the necessary precautions to avoid faulty conclusions. The results presented in paper II clearly illustrate that choice of ADD-values and population measurement highly affects the calculated antimicrobial consumption, both when viewed as a single point in time and when evaluating trends over years. This underlines the need to always disclose a detailed description of calculation method when reporting antimicrobial usage. The results of the study also demonstrate that demographics of a chosen population should always be considered carefully prior to analysis.

The results of study 3 indicate that lowering the antimicrobial consumption through punitive legislation might affect productivity and health negatively.

Sammendrag (summary in Danish)

Dette ph.d. projekts to overordnede formål var (i) at fremme forståelsen for VetStat data vedrørende grises antibiotikaforbrug, både i forbindelse med anvendelse i forskning og betydningen af standardiserede beregningsmetoder ved afrapportering, og (ii) at undersøge hvorvidt den hurtige reduktion af antibiotikaforbruget efter introduktionen af gult kort ordningen havde påvirket produktiviteten og sundheden i svineproduktionen. De to overordnede mål blev undersøgt i tre separate studier.

Studie 1

Det første studie var fokuseret på at beskrive den nuværende struktur af VetStat gennem interviews, samt et litteratur og et database studie. To hovedpublikationer blev identificeret og otte personer interviewet. Hovedsageligt er kompletheden og validiteten af VetStat data øget betragteligt siden Vetstats implementering i år 2000. Antibiotika solgt til anvendelse i svinebesætninger registreres primært af apoteker. På trods af en høj grad af validitet i de indberettede data fra apotekerne med hensyn til kvantitet og type af de solgte produkter, ses der dog stadig sporadisk fejl i en lille andel af registreringerne, som fx ugyldigt angivet aldersgruppe.

Studie 2

Det andet studie (artikel 1 + artikel 2) fokuserede på at beskrive et udvalg af de større udfordringer, man mødes af ved anvendelse af VetStat data til estimering af grises antibiotikaforbrug på nationalt og besætningsniveau.

Artikel 1 fokuserede på at beskrive et udvalg af de udfordringer og løsninger, der tilvejekommer i forbindelse med at det faktiske antibiotikaforbrug på besætningsniveau forsøges estimeret. De beskrevne udfordringer og løsningsforslag blev udvalgt og defineret under diskussionsmøder i en inter-institutionel gruppe bestående af seks ph.d. studerende og en adjunkt. Alle identificerede udfordringer kunne inddeles i to hovedkategorier: (i) udfordringer opstået på grund af datakvalitet eller databasens struktur, og (ii) udfordringer opstået i forbindelse med udregning af det faktiske antibiotikaforbrug og håndtering af data. Grundlæggende kunne alle større udfordringer tilskrives vanskeligheder opstået i forbindelse med at transformere sekundære salgsdata til en estimering af det faktiske forbrug. Vigtigheden af den enkelte udfordring var i høj grad afhængig af det pågældende forskningsspørgsmål.

Artikel 2 fokuserede på at undersøge i hvilken grad de valgte dyredose (ADD) værdier og mål for populationen påvirkede det beregnede nationale antibiotikaforbrug til grise med særligt fokus på trend over tid. Studiet blev udført som et retrospektivt, observationelt databasestudie.

die, hvor antibiotikaforbruget fra 2007 til 2013 blev undersøgt, beregnet som ADDer per gris per år baseret på (i) tre forskellige sæt af værdier for dosis per kg levende kropsvægt (ADD-værdier) anvendt af større danske institutioner, og (ii) fire forskellige mål for den danske svinepopulation. Deskriptiv statistik blev anvendt til præsentation af resultater. Der blev fundet markante variationer i resultater over tid, afhængigt af både det valgte sæt ADD-værdier samt populationsmål. Ændringen i ADD/gris/år fra 2007 til 2013, blev fundet til at variere mellem et fald på 11% til en stigning på 22% afhængig af den valgte udregningsmetode.

Studie 3

Det tredje studie (artikel III) blev udført som et retrospektivt, observationelt studie. Det blev undersøgt (i) hvorledes antibiotikaforbruget blev reduceret ifølge landmænd og dyrlæger, og (ii) hvorvidt reduktionen af antibiotikaforbruget efter introduktionen af gult kort ordningen havde påvirket produktivitet og sundheden i danske svinebesætninger, målt som dødelighed, daglig tilvækst, kødprocent ved slagt og slagteanmærkninger. I alt besvarede 202 besætninger og 58 dyrlæger spørgeskemaet om hvordan antibiotikaforbruget blev reduceret. De hyppigste svar var øget vaccination, mindre flok-medicinering og uddannelse af ansatte. Både besætninger med et højt antibiotikaforbrug og besætninger med et lavt forbrug reducerede deres antibiotikaforbrug efter introduktionen af gult kort ordningen. Hos fravænningsgrise sås der en signifikant højere dødelig (49 besætninger; 2,4% til 3,0%; $p=0,0001$) og en trend mod lavere daglig tilvækst (43 besætninger; 447 til 436 gram/dag;) med højere standard afvigelse (43,2 til 48,1; $p=0,56$). Hos slagtesvin blev der både set trends mod højere dødelighed (3,3% til 3,7%; $p=0,51$), lavere daglig tilvækst (890 til 867 gram per dag; $p=0,71$) og højere standard afvigelse for den daglige tilvækst (58,8 to 64,0; $p=0,43$). Slagtedata blev indhentet fra 75 besætninger. Kødprocenten steg signifikant (60,05 to 60,18; $p<0,0001$), men der sås ingen ændring i standard afvigelsen af kødprocent. Prævalensen af de 13 typer undersøgte slagtelæsioner blev undersøgt med en generaliseret mixed model for binomialt udfald med gris, batch og besætninger som levels. Der sås en signifikant stigning i prævalensen af lokaliserede halebid (OR=1,8), kronisk peritonitis (OR=1,3) og abscesser i hoved og øre (OR=1,2) ($p<0,0001$). Derimod faldt prævalensen af kronisk pleuritis (OR=0,9), abscesser i for- midt- og bagpart (OR=0,84), kronisk pneumoni (OR=0,8), abscesser i ben og klove (OR=0,7) og inficerede halebid (OR=0,4) ($p<0,0001$). Hverken prævalensen af osteomyelitis, kronisk enteritis eller kronisk infektiøs arthrititis ændredes signifikant.

Konklusioner

VetStat data repræsenterer en unik mulighed for at monitorere grises antibiotikaforbrug tæt – både på national- og besætningsniveau. Det er dog helt essentielt at holde sig for øje at VetStat er salgsdata og ikke forbrugsdata – og at fejl kan forekomme i data på alle niveauer. Det er således den enkelte forskers ansvar at tage de nødvendige forholdsregler for at undgå fejlagtige konklusioner. Resultaterne præsenteret i artikel II illustrerer tydeligt at valg af ADD-værdier og mål for populationen i høj grad påvirker det beregnede nationale antibiotikaforbrug, både beregnet som et punkt i tiden og evalueret henover en periode. Dette understreger

vigtigheden af altid at inkludere en detaljeret beskrivelse af beregningsmetoden, når antibiotikaforbruget rapporteres. Resultaterne i artikel II understreger også vigtigheden af nøje at overveje hvilke demografiske forhold der gør sig gældende for en valgt population inden videre analyser foretages.

Resultaterne fra studie 3 peger på, at en reducereing af antibiotikaforbruget gennem indførslen af straffende lovgivning muligvis kan have negative konsekvenser for svineproduktiviteten og sundheden på kort sigt.

List of abbreviations

ADD: Animal Daily Dose. ADD has been defined as the average maintenance dose per day for the main indication in a specified species (Jensen et al., 2004)

ADD-values: Assumed average maintenance dose per day per kilogram animal

- **VetStat ADD-values:** Set of ADD-values available in the VetStat database from 2001 and up until 30 November 2014, used prior to 30 November 2014 in relation to the yellow card initiative and in the DANMAP reports 2001-2011 to calculate antimicrobial usage in ADD.
- **DVFA ADD-values:** Set of ADD-values used from 30 November 2014 in relation to the yellow card initiative to calculate antimicrobial usage in ADD.
- **DANMAP ADD-values:** set of ADD-values used in the 2012 DANMAP report 2012 to calculate antimicrobial usage in ADD.

ATC: Anatomical Therapeutic Chemical. Used to describe the ATC classification system defined by the World Health Organization. According to the World Health Organization's ATC classification system, "*the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties*" (World Health Organization, 2011).

CHR: Central Husbandry Register. A Danish national database containing detailed animal population data at herd level (Anonymous, 2013).

DANMAP: The Danish Programme for surveillance of antimicrobial consumption and resistance in bacteria from animals, food and humans (DANMAP, 2011)

DDD: Defined Daily Dose. DDD is defined by the World Health organization as "*the assumed average maintenance dose per day for a drug used for its main indication in adults*" (World Health Organization, 2009).

DVFA: The Danish Veterinary and Food Administration. DVFA is a subdepartment under the Ministry of Environment and Food of Denmark. The Ministry of Environment and Food

was created in summer 2015, as a result of the fusion between the Ministry of the Environment and the Ministry of Food, Agriculture and Fisheries of Denmark (Møller-Olsen, 2016).

ESVAC: European Surveillance of Veterinary Antimicrobial Consumption (European Medicines Agency, 2016)

EU: European Union

SPC: Summary of Product Characteristics (European Commission, 2009)

SPF: Specific Pathogen Free

VetStat: The Danish Veterinary Medicines Statistics Program. VetStat is a national database containing herd level data on veterinary medicine sales (Stegge et al., 2003).

WHO: World Health Organization (World Health Organization, 2015a).

Definition of concepts

Antimicrobial: *“a substance acting primarily against bacteria”* (European Medicines Agency, 2013b).

Construct validity: *“refers to the degree to which a variable accurately reflects the phenomenon that it purports to measure”* (Motheral and Fairman, 1997) – e.g. the degree to which antimicrobial usage according to VetStat reflects actual antimicrobial usage.

Curative treatment: *Treatment of an ill animal or group of animals, when the diagnosis of disease or infection has been made* (European Platform for the Responsible Use of Medicines in Animals, 2013).

Finisher: A pig kept for slaughter weighing above 30 kg.

Herd: *“A gathering of animals of the same species used for a specific purpose, which is attached to a specific geographical location”* (translated from Danish) (Anonymous, 2013).

Prophylaxis: *“the administration of antimicrobial drugs for preventive measures”* (Timmerman et al., 2006).

Metaphylaxis: *“The application of antimicrobials to groups of animals at times when only single animals of the group present symptoms of the disease, but it is expected that most of the group will become affected”* (Schwarz et al., 2001).

Median Odds Ratio (MOR): *“The MOR is defined as the median value of the odds ratio between the area at highest risk and the area at lowest risk”* (Merlo et al., 2006). Explained differently: *“The MOR quantifies the variation between clusters (the second-level variation) by comparing two persons from two randomly chosen, different clusters. Consider two persons with the same covariates, chosen randomly from two different clusters. The MOR is the median odds ratio between the person of higher propensity and the person of lower propensity”* (Larsen and Merlo, 2005).

Secondary data: *“If the data set in question was collected by the researcher (or a team of which the researcher is a part of) for the specific purpose or analysis under consideration, it is*

primary data. If it was collected by someone else for some other purpose, it is secondary data” (Boslaugh, 2007).

Secondary databases: A database where secondary data is collected (Harpe, 2009).

Weaner: Pig from weaning until 30 kg bodyweight.

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1 Introduction

The relation between antimicrobial usage and emergence of antimicrobial resistance has been confirmed in several scientific papers and reports (Aarestrup and Wegener, 1999; McEwen and Fedorka-Cray, 2002; Asai et al., 2005; Emborg et al., 2007; European Centre for Disease Prevention and Control and European Medicines Agency, 2009). Potentially, transmission of antimicrobial resistant bacteria from animals to humans may affect human health negatively (Endtz et al., 1991; World Health Organization, 2001; Angulo et al., 2004; Khanna et al., 2008; European Medicines Agency, 2014). As a result, several influential international institutions have advocated for the need to monitor veterinary antimicrobial usage (European Medicines Agency, 1999; Nicholls et al., 2001; World Health Organization, 2001; Council of the European Union, 2008).

As the first country in the world, Denmark launched a nation-wide program in 2000, collecting detailed data on medicine distribution at herd level (Stege et al., 2003). The program and the affiliated database are known collectively as the Danish Veterinary Medicines Statistics Program (VetStat) (Vieira et al., 2009). VetStat has since its implementation served as a secondary data source in several pharmaco-epidemiological research studies (Emborg et al., 2007; Jensen et al., 2010; Vigre et al., 2010; Hybschmann et al., 2011; Agersø and Aarestrup, 2012) and enabled detailed annual reports on national veterinary antimicrobial consumption (DANMAP, 2001). VetStat data have also facilitated implementation of the antimicrobial restrictive legislation, dubbed “the yellow card” (Aarestrup, 2012) – hereafter referred to as the yellow card initiative. The yellow card initiative penalizes pig herds, whose antimicrobial consumption exceeds governmentally set threshold values (Alban et al., 2013). In Denmark, the pig production’s antimicrobial usage has in particular been targeted, as the production of pigs is quite substantial. In 2012, Denmark produced 29.1 million (Danish Agriculture and Food Council, 2016), which accounted for 76% of the total veterinary antimicrobial consumption of 112 tonnes active ingredient (DANMAP, 2012b), corresponding to 44 mg active ingredient/kg biomass (European Centre for Disease Prevention and Control et al., 2015). In comparison the human population amounted to 5.6 million Danish inhabitants (Østberg, 2016) with an antimicrobial usage of 136 mg active ingredient/kg biomass (European Centre for Disease Prevention and Control et al., 2015).

Following the introduction of the yellow card initiative in 2010, a rapid 25% reduction was seen from 2009 to 2011 in the average amount of antimicrobials sold per produced pig in Denmark (Jensen et al., 2014). To the author’s knowledge, Denmark is presently the only country in the world who has instigated this type of punitive bench-marking legislation at

herd level. The pioneering nature of these efforts gives rise to unique inquiries into the potential consequences of this type of legislation. In particular a wish arose to determine whether the rapid lowering of antimicrobial consumption from 2009 to 2011 had affected pig health and productivity.

Since VetStat launched in 2000, a number of developments have occurred, which could potentially affect findings based on VetStat data. Among these developments are namely a diversification in how consumption is calculated and a changing demographic in the pig production. Within the yellow card initiative, herd antimicrobial exposure is calculated as “number of standardized treatments per 100 animals per day”, also known as Animal Daily Doses (ADDs)/100 animals/day (Anonymous, 2014a).

Prior to 2012, all major Danish institutions applied the same standardized dosages when quantifying the consumption in number of ADDs based on VetStat data (Anonymous, 2010; DANMAP, 2011).

However, in recent years two new methods for assigning standardized dosage values have surfaced. One method was introduced by the Danish Veterinary and Food Administration (DVFA) in 2014 (Anonymous, 2014a), another was introduced by the Danish Programme for surveillance of antimicrobial consumption and resistance in bacteria from animals, food and humans (DANMAP) in the DANMAP 2012 report (DANMAP, 2012a). Alongside changes in the assignment of standardized dosage values when calculating consumption in ADDs, a shift has occurred in the Danish pig production: Compared to the production pattern in 2000, a much larger percentage of the produced pigs are now being exported live to neighbouring countries, primarily as 30 kg pigs (Hansen and Zobbe, 2014). Whether or not exported pigs are included when the national pig production are tallied up may therefore have a greater impact on the calculated results than what was previously the case.

While several papers have been published based on VetStat data (Emborg et al., 2007; Vieira et al., 2009; Hybschmann et al., 2011; Jensen et al., 2014), none have yet provided an in-depth description of the challenges encountered when attempting to estimate actual antimicrobial exposure based on VetStat data together with corresponding solutions. For researchers new to VetStat, the lack of easily accessible guidance might increase the risk of misinterpreting results. A need was therefore identified to promote understanding of VetStat data, the applied calculation procedures and to determine whether the shift in calculation procedures affected the calculated national pig antimicrobial consumption.

1.1 Scientific aims

The overall aims of the PhD thesis were:

- To aid understanding of (i) VetStat data on pig antimicrobial usage; (ii) the factors at play when reporting pig antimicrobial consumption based on VetStat data; and (iii)

let the describing of (i) and (ii) serve as information and inspiration for relevant parties in other countries considering similar work

- To investigate (i) how the reduction in pig antimicrobial consumption, following introduction of the yellow card initiative, had been achieved according to farmers and veterinarians; and (ii) whether pig productivity and health had changed in relation to the aforementioned decrease in antimicrobial consumption.

The first study centered on describing the present structure of VetStat.

The second study (paper I + paper II) focused on delineating major challenges encountered when using VetStat data to estimate national and herd level pig antimicrobial consumption. More specifically, paper I focused on describing a select set of challenges encountered when attempting to estimate actual herd antimicrobial consumption and propose corresponding solutions. Paper II focused on investigating to which degree (i) chosen Animal Daily Dose (ADD) assignment method for standardized dosage values and (ii) choice of population measurement influenced the calculated national pig antimicrobial consumption with a specific emphasis on trend over time.

The third study (paper III) investigated (i) how the reduction in antimicrobial consumption had been achieved according to veterinarians and farmers; and (ii) whether the rapid decrease in antimicrobial consumption following introduction of the yellow card initiative had affected pig productivity and health, measured as mortality, daily weight gain, lean meat percent and lesions at slaughter.

1.2 Outline of thesis

This PhD thesis consists of eight chapters and four appendix sections.

Chapter 1 (this chapter) contains a general introduction to the PhD thesis, scientific aims and outline of the thesis.

Chapter 2 contains a theoretical introduction to the three main topics covered in this thesis: (i) a brief introduction to VetStat; (ii) measurement units applied when reporting veterinary antimicrobial usage; and (iii) a description of current benchmark initiatives instigated at national level to reduce pig antimicrobial consumption and an overview of changes in productivity related to the cessation of antimicrobial growth promoter use in Northern European countries. In addition, a brief description is given of the methods applied when estimating veterinary antimicrobial consumption.

Chapter 3 outlines research activities performed in the PhD project.

Chapter 4 contains additional information on VetStat obtained in study 1, which was not presented in chapter 2 or in one of the scientific papers of this PhD thesis. Results were first presented in a written assignment produced in relation to the MSc Programme in Veterinary Medicine course “*Animal Health Research and Health Promotion*”, the Master’s thesis of the author of this PhD thesis (title: “*Reporting antimicrobial consumption in Danish pigs – Effect of calculation methods*”) and the conference paper: “*Vetstat – Monitoring usage of antimicrobials in animals*“, presented at the ICAR Conference 2013, Århus, Denmark. The chapter also contains a summary of the results presented in the three papers (I-III).

Chapter 5 presents the central scientific work of the PhD project:

- A. Paper I: Improving institutional memory on challenges and methods for estimation of pig herd antimicrobial exposure based on data from the Danish Veterinary Medicines Statistics Program (VetStat).
- B. Paper II: Reporting the national Danish pig antimicrobial consumption: Influence of assigned daily dosage values and population measurement.
- C. Paper III: Changes in productivity and health in Danish weaners and finishers following introduction of the “yellow card” antimicrobial legislation.

Chapter 6 contains a general discussion of the results presented in the three papers. Furthermore additional subjects are addressed, which were not at all or only briefly addressed in the papers. Important points mentioned in the three papers are repeated if they were deemed essential for understanding of the results and elaborated on where necessary.

Chapter 7 and 8 contain conclusions and perspectives of the PhD thesis, respectively. Abbreviations may differ between the thesis itself and the included scientific papers.

2 Background

2.1 Estimation of veterinary antimicrobial usage

Today a wide range of methods are applied when estimating both country and herd antimicrobial consumption. Examples of ways to estimate national antimicrobial consumption are data from detailed national databases, such as VetStat (Jensen et al., 2004), or via total sales data from primary manufacturers, wholesalers and importers (European Medicines Agency, 2015d). Other options include collection of data from abattoirs, if each animal is accompanied by a corresponding treatment sheet (Chauvin et al., 2005), from veterinarians, as e.g. information on treatment practices or assessment of treatment records (Jordan et al., 2009), or directly from the herds, as e.g. questionnaires, treatment records or purchase receipts (Rosengren et al., 2008). However, these methods may be better suited for studies on usage patterns than studies where complete national consumption is pursued, as they typically cover just a small subset of the target population (Sawant et al., 2005; Callens et al., 2012).

Since 2003, the European Union (EU) has required its member states to monitor antimicrobial resistance in selected bacteria (European Commission, 2003). Presently, no corresponding EU directive exists on surveillance of veterinary antimicrobial consumption. Yet in 2010, the European Medicines Agency launched the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) program on request from the European Commission (European Medicines Agency, 2016). The ESVAC program collects overall national antimicrobial consumption from voluntarily participating EU member states (European Medicines Agency, 2013a) with findings published in annual reports (European Medicines Agency, 2015d).

Despite increased attention to data on veterinary antimicrobial usage, the introduction of large national databases containing herd level information remains a relatively recent phenomenon. In 2000, Denmark was the first country in the world to introduce a database containing detailed medicines sales data at herd level with nation-wide coverage (Stege et al., 2003). Through the 2000s, no similar databases were introduced in any other EU country. However, several papers were published attempting to estimate national veterinary antimicrobial consumption based on subsamples of the target population (Chauvin et al., 2002; Sawant et al., 2005; Timmerman et al., 2006; Pol and Ruegg, 2007; Jordan et al., 2009; González et al., 2010). In 2011, the Netherlands introduced a database similar to VetStat, though limited to data on production animals (Bos et al., 2013; the Netherlands Veterinary Medicines Authority, 2015). In 2014, the Belgian industry organization Belpork followed suit and began collecting antimicrobial usage data for herds participating in their quality assurance

schemes (Lagast, 2015). The Belgian government recently announced plans to expand Belpork's registrations by introducing mandatory registration at herd level of all antimicrobial usage in veal calves, poultry and pigs (W. Vanderhaeghen, personal communication).

Despite the recent initiatives in the Netherlands and Belgium, the vast majority of countries still rely on data from wholesalers when estimating national veterinary antimicrobial consumption (European Medicines Agency, 2015d). However, an increasing number of countries have shown interest in developing databases similar to VetStat in recent years (European Medicines Agency, 2013c, 2015c; van Rennings et al., 2015).

2.1.1 A brief description of VetStat

2.1.1.1 History

In 1998, Denmark hosted the invitational EU conference "The Microbial Threat". The conference and associated workshop led to publication of "The Copenhagen Recommendations". Among the recommendations was a call for increased monitoring of veterinary antimicrobial consumption (Rosdahl and Pedersen, 1998). Two years later, in 2000, the national surveillance program on veterinary medicine usage, VetStat, was implemented as a result of a combined political and scientific determination. The database was developed in close collaboration between both industrial and governmental sectors (Stege et al., 2003). VetStat was created with four central goals: *"(1) to monitor veterinary usage of drugs in animal production; (2) to help practitioners in their work as herd advisors; (3) to provide transparency as a basis for ensuring compliance with rules and legislation and (4) to provide data for pharmaco-epidemiological research"* (Stege et al., 2003). The database VetStat was built as a relational database on an Oracle platform (Stege et al., 2003). The implementation of Vetstat was enabled by several factors, such as (i) an already existing legislation assigning a unique identification number to each production animal herd (Anonymous, 1995b); (ii) no over-the-counter sale of antimicrobials; and (iii) veterinary antimicrobials to end-users solely being sold from pharmacies, feed mills or veterinary practitioners. VetStat is currently owned and managed by the Ministry of Environment and Food of Denmark.

2.1.1.2 Content of VetStat

VetStat contains detailed sales data on all veterinary prescription medicine. Consequently, all sales of antimicrobial products are included, as these can only be obtained through veterinary prescription (Anonymous, 2015b). By law, pharmacies, feed mills and veterinary practitioners are obligated to report sales data to VetStat. Pharmacies and feed mills report sales data and veterinary practitioners report medicine sold and used in clinical practice for production animals (Stege et al., 2003). When an antimicrobial product for use in pigs is sold, the corre-

sponding VetStat data entry always states: date of sale, quantity of product sold, Nordic commodity number of the product (used to identify a specific individual packaging of a product down to concentration, trade name, formulation and size), prescribing veterinarian, identification number on registering entity and which herd, animal species, age group and disease group the product has been prescribed for (Jensen et al., 2004). An overview of the animal species, age groups and disease groups occurring in VetStat data is displayed in Appendix I. VetStat is described in closer detail in chapter 4.1 and paper I.

2.1.2 Data validity on national databases

It has been recommended that research projects based on secondary data from large scale databases should always include a thorough assessment of database procedures and data validity (Ray, 1997; Kozyrskyj and Mustard, 1998; Polinski et al., 2009). Within the field of human medicine, the challenges most commonly described are related to (i) ease of access, (ii) completeness of data, (iii) incorrectly entered data and (iv) discrepancy between what is registered in the database and actual events (Sørensen et al., 1996; Schneeweiss and Avorn, 2005; Häyrynen et al., 2008; Johannesdottir et al., 2012). However to the author's knowledge, an in-depth description has yet to be published on challenges encountered when working with secondary data from veterinary medicine sales databases.

2.1.3 Measurement units applied

Several types of measurement units have been described for reporting veterinary antimicrobial consumption (Chauvin et al., 2001). Among these are money spent on medicine (Chauvin et al., 2008), kg of active ingredient (Grave et al., 2010), number of prescriptions (Holso et al., 2005), used daily dose (Callens et al., 2012), prescribed daily dose (Pardon et al., 2012) and ADD (Jensen et al., 2004; Timmerman et al., 2006). ADD is inspired by the World Health Organization (WHO) unit "*defined daily dose*" (DDD) (Jensen et al., 2004). Within human medicine, DDD is the unit most commonly used when reporting antimicrobial usage. WHO has defined DDD as "*the assumed average maintenance dose per day for a drug used for its main indication in adults*" (World Health Organization, 2009). Only one DDD is assigned by WHO per route of administration within the Anatomical Therapeutic Chemical (ATC) classification system (Wertheimer, 1986). DDDs are freely available online on WHO's website (World Health Organization, 2015b). DDD is strictly a technical unit, it may therefore deviate from actual dosage prescribed or recommended (World Health Organization, 2009).

In Denmark, the two most prevalent measurement units used to report veterinary antimicrobial consumption are kg of active ingredient and ADD (Emborg et al., 2007; DANMAP, 2009; Hybschmann et al., 2011). ADD has been defined as the average maintenance dose per day for the main indication in a specified species (Jensen et al., 2004). ADD is, as DDD, a theoretical unit developed to standardize reports on medicine consumption (Timmerman et al., 2006). Differences may therefore occur between ADD and actual number of dosages used or actual number of dosages prescribed (Pardon et al., 2012). In Denmark, an assumed aver-

age maintenance dose per day per kilogram animal (ADD-value) is listed for each antimicrobial product (Jensen et al., 2004). Presently, a total of three different sets of ADD-values have been developed for use when reporting antimicrobial usage based on VetStat data: (i) the set of ADD-values available in VetStat from 2001 and up until 30 November 2014, used prior to 30 November 2014 in relation to the yellow card initiative and in the DANMAP reports 2001-2011 (VetStat ADD-values) (DANMAP, 2001, 2011); (ii) the set of ADD-values used from 30 November 2014 in relation to the yellow card initiative (DVFA ADD-values) (Anonymous, 2014a); and (iii) the set of ADD-values used in the 2012 DANMAP report (DANMAP ADD-values) (DANMAP, 2012a).

In order to facilitate comparisons between countries, ESVAC is currently developing its own set of ADD-values. This is done to enable reports on antimicrobial consumption in “defined daily dose for animals”. ESVAC call their measurement unit DDDvet and, like the Danish ADD-value, also define it as “*the assumed average dose per kg animal per species per day*” (European Medicines Agency, 2015b). DDDvet is based on the dosage stated in each product’s Summary of Product Characteristics and is also inspired by the WHO DDD unit (European Medicines Agency, 2015b).

2.1.4 Change in the Danish pig production

The Danish pig industry has since the 1990s gone from primarily slaughtering all produced pigs nationally to exporting a large share of the produced pigs live (Orr and Shen, 2006; Hansen and Zobbe, 2014). In 1995, 2% of the total number of pigs produced were exported live (Larsen, 2016). In 2014, the number of exported live pigs accounted for 33% of the total Danish pig production, as a result of both a decrease in the nationally slaughtered pigs and an increase in the export of live pigs (Larsen, 2016). At export, 90% of the pigs weigh in the vicinity of 30 kg (Hansen and Zobbe, 2014). In ADD, 7-30 kg pigs accounted for 77% of the total Danish pig antimicrobial consumption in 2011 (DANMAP, 2011).

2.2 Initiatives implemented to reduce pig antimicrobial usage

2.2.1 Initiatives implemented in Denmark

To heighten prudent usage of veterinary antimicrobials, publication of standard treatment guidelines (Nuotio et al., 2011; Nielsen et al., 2013; Sveriges Veterinärmedicinska Sällskap, 2013) and declaration of a clear political goal to reduce antimicrobial usage (Anonymous, 2012; Bos et al., 2013; De Graef, 2014; Nielsen, 2015) have been two of the most commonly implemented national level initiatives across European countries.

In addition to these two initiatives, Denmark has implemented several measures to reduce antimicrobial usage in the pig production. In the mid-1990s, legislative restrictions were introduced on veterinary profits from medicine sales and maximum allowable time of treatments after prescription. Furthermore, prophylactic use of antimicrobials was banned and pharmaceutical companies were prohibited from offering financial incentives to further sales (Aarestrup et al., 2010). Legislation was also introduced to encourage health advisory agreements between farmers and veterinarians, entailing a set amount of mandatory veterinary visits per annum (Anonymous, 1995a). From 1995 to 1998, bans were imposed on various types of antimicrobial growth promoters used in the food animal production (World Health Organization, 2002). This was motivated by increasing scientific evidence linking antimicrobial growth promoter usage in food animals to antimicrobial resistance in potential human pathogens (Hammerum et al., 2007). In response to a growing public concern, the Danish pig industry decided to voluntarily cease all use of antimicrobial growth promoters in finishers in 1998 and in weaners in 1999 (World Health Organization, 2002). The implemented penalty tax for use of antimicrobial growth promoters in finishers further encouraged this decision (Jensen, 2003). In 1998, the Danish cattle and poultry industry also implemented a complete voluntary stop on antimicrobial growth promoter use (World Health Organization, 2002).

The year 2010 saw the instigation of two other major initiatives. Firstly, the Danish pig industry self-imposed a voluntary stop on the use of all cephalosporins (Agersø and Aarestrup, 2012). Secondly, the Danish government introduced legislation, benchmarking pig herds' antimicrobial consumption and penalizing high consumers (Anonymous, 2010). Since 2010, the latest released initiatives have been in relation to the second Veterinary Settlement, introducing mandatory laboratory diagnostics and an increased number of veterinary visits in conjunction with oral group medication in 2014 (Ministry of Food, Agriculture and Fisheries, 2012; Anonymous, 2014b).

2.2.2 Benchmark initiatives implemented to reduce pig antimicrobial usage

It is still relatively seldom that benchmarking systems are implemented to decrease herd antimicrobial usage, as they require detailed data on herd antimicrobial usage. To the author's knowledge, benchmarking systems on herd level antimicrobial usage have so far been introduced in three countries: the Netherlands, Belgium and Denmark.

In the Netherlands, a plan was implemented in 2010 to reduce national live stock antimicrobial usage by 50% within a 4-year period (Ministry of Economic Affairs, 2014; Speksnijder et al., 2015b). One of the elements planned to aid in the reduction was a new benchmark system, pinpointing production animal herds with a high consumption of antimicrobials. Benchmark threshold values on pig antimicrobial consumption were decided in 2012 by the Netherlands Veterinary Medicine Authority. The threshold values were decided based on the distribution of consumption, targeting sow and pre-weaning pig herds above the 75th percentile and herds with fattening pigs above the 90th percentile (the Netherlands Veterinary Medicines Authority, 2014). According to present Dutch legislation, herds with an antimicro-

bial usage above the set threshold value are obligated to implement antimicrobial reducing initiatives, but are not directly penalized in a financial manner (Bos et al., 2013). Total sales of antimicrobials for use in animals (tonnes) decreased by 56% from 2007 to 2012 (Speksnijder et al., 2015b).

The benchmarking system in Belgium was initiated by the pig industry organization Belpork in 2014 (De Graef, 2014). At its implementation, the benchmarking system exclusively concerned herds enrolled in Belpork's quality program. In 2015, enrolled herds covered 60% of all Belgian pig herds (Lagast, 2015). In the benchmarking system, farmers receive reports on their antimicrobial consumption every 6 months. Farmers with an antimicrobial consumption in the top ten percentile are obligated to make an analysis of their use, including a plan on how to reduce their antimicrobial consumption (W. Vanderhaeghen, personal communication).

The benchmarking system in Denmark was implemented in December 2010. The system differentiates itself from the Belgian and Dutch by being run solely by the governmental institution DVFA. DVFA enforces the governmentally defined threshold values by imposing predefined penalties on pig herds, whose antimicrobial usage exceed said threshold values (Anonymous, 2010). At the introduction of the benchmarking system, penalties initially included a fine, restrictions dictating that oral group medication could not be re-prescribed more than once and a call to lower usage within nine months (Petersen and Larsen, 2010). Failing to lower the antimicrobial usage within nine months triggered several other restrictions, such as more frequent veterinary visits, implementation of vaccination strategies and potentially visits by a second opinion veterinarian – all paid for by the farmer in question (Jensen et al., 2014). However, since June 2014 penalties have changed. According to present legislation, herds are now subject to penalties for a minimum period of two years after being pinpointed as a high user. Among the added restrictions are a halving of the allowable time period between mandatory veterinary visits and between laboratory diagnostics, if the herd wishes to be able to initiate treatment with oral antimicrobials of a disease known to be present in the herd without a veterinarian present (Danish Veterinary and Food Administration, 2014). All is paid for by the farmer (Danish Veterinary and Food Administration, 2014). The penalties imposed on high-consumer herds have been dubbed “yellow cards”. In previous peer-review papers, the legislation has also been referred to as “the “Yellow Card” legal intervention” (Jensen et al., 2014) and “the “yellow card” antimicrobial scheme” (Alban et al., 2013). In this PhD thesis, the legislation is referred to as “the yellow card initiative”. As previously mentioned in the Introduction chapter, a 25% decrease in the antimicrobial consumption per pig produced was seen from 2009 to 2011 (Jensen et al., 2014).

2.2.3 Productivity and health consequences following a national reduction in antimicrobial usage

In 2013, Alban et al. published a study investigating whether the prevalence of lesions at slaughter had changed after implementation of the yellow card initiative. The study reported

an increase in some types of lesions (chronic peritonitis, chronic enteritis, osteomyelitis, umbilical hernia and the risk of carcass condemnation), but also found a decrease in the prevalence of chronic pleuritis and chronic pneumonia. The decrease was thought to be related to an increase in vaccines sales (Alban et al., 2013). Apart from the paper by Alban et al. in 2013, no other papers have been published investigating potential productivity and health consequences following a rapid decrease in pig antimicrobial consumption in relation to implementation of national punitive antimicrobial restrictive legislation. However, a similar rapid decrease in the national Danish veterinary antimicrobial consumption was seen in relation to the cessation of antimicrobial growth promoter usage, where the overall usage of veterinary antimicrobials decreased by 47%, from approximately 200 tonnes in 1994 to approximately 103 tonnes in 2004 (Bengtsson and Wierup, 2006). Results presented on pig health and productivity consequences following cessation of antimicrobial growth promoter usage in Denmark, Sweden and Finland will be covered in the following subchapters.

2.2.3.1 Denmark – health and productivity following cessation of antimicrobial growth promoter use

In a study covering approximately 11% of all Danish pig herds, weaner mortality was found to have increased from 2.9% in 1998 to 3.5% in 2000. During the same time span, weaner daily weight gain was found to have decreased from 427 grams per day to 411 grams per day (World Health Organization, 2002; Kjeldsen and Callesen, 2006). In a long-term perspective, weaner mortality continued to increase to 4.4% in 2004, but thereafter steadily declined, reaching a 2.7% mortality in 2008 (Aarestrup et al., 2010; Vinther, 2011). From 2002 until 2008, average daily weight gain generally increased, reaching 425 grams per day in 2004 and 463 gram per day in 2008 (Aarestrup et al., 2010; Vinther, 2011).

For finishers, the overall national average for mortality and daily weight gain were not found to be affected by the cessation of antimicrobial growth promoter usage. However, in a subsample of 62 finisher herds, a reduction in daily weight gain and an increase in the occurrence of diarrhea were experienced as temporary problems in 26% of the herds and as permanent problems in 11% of the participating herds (Callesen, 2004).

Treatment incidence of diarrhea was found to increase sharply in both weaners and finishers in the first months immediately following the cessation of antimicrobial growth promoter use, with some farms reporting severe difficulties controlling post-weaning diarrhea (World Health Organization, 2002). One year after the initial cessation of antimicrobial growth promoter usage, weaner treatment incidence of diarrhea was still elevated, whereas finisher treatment incidence had reverted back to the level observed prior to the cessation of antimicrobial growth promoter usage (Larsen, 2004).

It was estimated that productivity losses due to the cessation of antimicrobial growth promoter use in the pig industry led to an increased production cost of 7.75 DKK per produced

pig (Jacobsen and Jensen, 2004). Initial analyses on long-term consequences predicted a decrease in the total pig production (Jacobsen et al., 2006). However from 1995 to 2008, total number of annually produced pigs increased from 20.3 million to 27.1 million pigs (Larsen, 2016).

2.2.3.2 Sweden – health and productivity following cessation of antimicrobial growth promoter use

Following cessation of antimicrobial growth promoter use, a Swedish study in 220 pig herds reported a 1.5 percentage point increase in weaner mortality in the year immediately following the stop on antimicrobial growth promoter use. In addition, a decrease in weaner daily weight and an increase in post-weaning diarrhea were observed (Robertsson and Lundeheim, 1994; Wierup, 2001). In addition, Wierup found that number of days until a 25 kilogram body-weight was reached increased by 5-6 days. No changes in pre-weaning mortality or finisher productivity were observed. In a long-term perspective, Wierup found that weaner mortality and days until 25 kg had decreased following the initial first year after the cessation of antimicrobial growth promoter use, however both were still at higher values than prior to the cessation of antimicrobial growth promoter use (Wierup, 2001).

2.2.3.3 Finland – health and productivity following cessation of antimicrobial growth promoter use

In a Finnish study performed in 73 pig herds, no significant change in the prevalence of weaner diarrhea was identified following the cessation of antimicrobial growth promoter use. Of these, 31 herds adhered to regular *Escherichia coli* vaccination schemes in the sows, 24 herds vaccinated only gilts or had more irregular vaccinations and 18 herds did not vaccinate against *E. coli* at all. On average weaners in the study were weaned at 34 days of age (Laine et al., 2004).

3 Research activities in the PhD project

3.1 Study 1: description of the present structure of VetStat

The first study (paper I) centered on describing the present structure of VetStat. A literature study was performed in combination with a series of interviews. This was supplemented with a retrospective, observational database study, which investigated: (i) cattle antimicrobial consumption from 2007 to 2011 according to two different estimation methods, and (ii) annual pig antimicrobial usage from 2002 to 2013 according to reporting entity and age group. The investigation into Danish cattle antimicrobial consumption was included to investigate completeness of VetStat data submitted by veterinarian practitioners. Approximately half of the cattle antimicrobial consumption is registered by the veterinary practitioners (DANMAP, 2009). For pigs, less than 2% of the total amount is registered by veterinary practitioners (DANMAP, 2009). Results are presented in chapter 4.1 of this PhD thesis. Additionally, results from study 1 formed the author's initial knowledge foundation on VetStat for paper I-III.

3.1.1 Literature study

The applied search engines were CAB abstracts, PubMed and Google Scholar. Search terms used were: VetStat, Danish or Denmark and antibiotic or antimicrobial. In addition, a search on the word "VetStat" was performed on two additional platforms: the website www.retsinformation.dk containing both historic and current documents on Danish legislation and in the Danish Veterinary Association's archive on its monthly publication "Dansk Veterinærtidsskrift". For all searches, only documents published prior to 6 April 2013 were included.

3.1.2 Interviews

Experts on VetStat were interviewed to collect information on the structure of Vetstat, including data management processes and submission of sales data to VetStat.

Government employees as well as scientific researchers were interviewed. All interviewees were working with VetStat or related national databases at the time of their interview. All contacted persons agreed to participate in an interview. In total, eight people were interviewed. All interviews were held as personal one to one meetings. The interviewer was always the author of this PhD thesis. Following an interview, interviewees were asked to read

minutes from the meetings to identify potential misunderstandings. Where necessary, information from interviews was supplemented with information gained through email correspondence.

Interviewees were asked questions on which data were submitted to VetStat, how and when. Interviewees were also asked, whether data were subjected to data management procedures after submission into VetStat. If the answer was yes, the interviewees were asked to elaborate on the subject. In addition, interviewees were asked how they calculated antimicrobial consumption based on VetStat data. Where conflicting statements on VetStat content and procedures were given by two interviewees, two VetStat data extractions were evaluated for that specific topic - one extracted February 2011 and one extracted May 2012. Separate data extractions were evaluated to minimize the risk of errors in the data extraction process affecting findings. If it was not possible to ascertain clarity based on an evaluation of Vetstat data extractions, Logica employees were consulted (www.cgi.dk). Logica is responsible for all software programming of VetStat. Where conflicting statements on other subjects were given, at least two other independent sources were needed to verify which statement was correct. One peer-reviewed paper accounted for one independent source, if the person initially stating the comment did not figure on the list of authors. The second independent source had to be a peer-reviewed paper by completely different authors or an interviewee from a different organization. The confirming or de-confirming interviewees were not informed of who had made the original statement.

The majority of interviews were performed between 2011 and 2014. To ensure that the description of the VetStat database structure, management processes and submission of data was up to date, Erik Jacobsen, a key figure regarding VetStat knowledge (DVFA-employee working intimately with VetStat from its inception to his retirement in December 2015), was asked to read and comment on an excerpt of the conference paper “*Vetstat – Monitoring usage of antimicrobials in animals*“, paper I in its entirety and a preliminary draft of paper II prior to submission. To adjust for any potential changes in VetStat following Erik Jacobsen’s retirement, Laura Mie Jensen, present DVFA employee working with VetStat, also read and commented paper I.

3.1.3 Supplementary retrospective, observational database studies on antimicrobial usage

Cattle antimicrobial consumption from 2007 to 2011 was investigated using a VetStat database extraction from 12 November 2012.

As an example of the historic development in registration of VetStat data on pig antimicrobial usage, an overview table was made of the annual pig antimicrobial usage according to reporting entity and age group. Antimicrobial usage was calculated in kilogram of active ingredient. All entries from 2002 to 2013 were included if the product sold was registered for use in pigs and sold directly to a herd. Registering entity type was either pharmacy, feed mill or veterinary

practitioner. Age group category was either (i) weaner, (ii) finisher, (iii) pre-weaning pigs and breeding animals or (iv) invalid age group. An entry with an invalid age group was an entry where the product was sold for use in pigs but the stated age group was neither weaner, finisher nor pre-weaning pigs and breeding animals. The VetStat data extraction for the overview table was performed October 2014.

3.2 Study 2: challenges encountered when using VetStat data to estimate pig antimicrobial usage (paper I and paper II)

The second study focused on delineating major challenges encountered when attempting to use VetStat data to estimate national and herd level antimicrobial consumption in pigs and propose corresponding solutions. Results are presented in paper I and paper II.

3.2.1 Challenges and corresponding solutions in relation to using VetStat data for estimation of pig herd antimicrobial exposure (paper I)

As described in paper I of this PhD thesis, challenges encountered when attempting to estimate actual herd antimicrobial exposure based on Vetstat data and the corresponding solutions were formulated in an interinstitutional group consisting of six PhD students and one Assistant Professor. Two of the participating members had previous experience as veterinarians in Danish swine practice. Originally, the group was formed to meet a need for interinstitutional communication. At the time of the group's formation, each group participant was performing research based on VetStat data. However, no organized knowledge sharing had previously existed between researchers involved in different projects using VetStat data. The initial aim of the group was therefore to bridge knowledge gaps, share experiences and develop a uniform method of VetStat data handling. After three initial meetings, a common wish was expressed to make the group members' experiences and knowledge available to other researchers. All challenges and solutions presented in the paper were discussed separately until a unanimous agreement was reached. A decision was made not to include numbers on different data inconsistencies and errors in the paper itself. This was done, as the impact of each challenge on research findings is highly dependent on the research question. A show-cased number might lead researchers to falsely dismiss a challenge as inconsequential for their particular research. Whereas, on the contrary, the purpose of this paper was to motivate researchers to evaluate their own specific dataset and assess each challenge's potential impact on their specific findings. An overview of group members' present research projects is shown in Appendix II.

3.2.2 Influence of assigned daily dosage values and population measurement in relation to estimation of national pig antimicrobial use (paper II)

The second paper was performed exclusively as a retrospective, observational database study. Data on antimicrobials sold for use in pigs from 1 January 2007 to 31 December 2013 were collected from VetStat (data extraction 31 March 2014). Data on ADD-values were collected from VetStat, the VetStat website and employees working with the DANMAP-reports. Data on number of pigs were collected from the Central Husbandry Register (CHR) (number of pig registered in the herds at any given time (Anonymous, 2013), Statistics Denmark (number of pigs in Denmark according to the annual summer count) and the industry organization Danish Agriculture and Food Council's annual publications on the production of pigs and pork (pigs slaughtered in Denmark and pigs produced in Denmark (pigs slaughtered + pigs exported live at ≥ 15 kg)). An overview is shown in Table 3.1. ADD was defined as the assumed average daily maintenance dose for the main indication in a specified species in accordance with previous publications on Danish pig antimicrobial usage (Jensen et al., 2004; Hybschmann et al., 2011) and Danish legislation (Anonymous, 2014a). Following calculation of number of ADDs per pig using the different values for standard dosages and population, respectively, results were then illustrated in graphs and descriptive statistics were presented.

Table 3.1. Data sources and information collected in relation to paper II.

Data source	Information collected
VetStat	Antimicrobials sold for use in pigs registered by pharmacies, feed mills and veterinary practitioners VetStat standard dosage values (ADD-values) applied in relation to the yellow card initiative prior to 30 November 2014
https://vetstat.dk	Standard dosage values (ADD-values) applied in relation to the yellow card initiative from 30 November 2014
National Food Institute, Technical University of Denmark	Standard dosage values (ADD-values) applied by DANMAP in the 2012 DANMAP report
Central Husbandry Register	Number of pigs registered per herd according to animal species and age group
Statistics Denmark	Total number of pigs in Denmark according to Statistics Denmark's annual summer count based on a subsample of 2,500 pig herds
Danish Agriculture and Food Council	Annual number of pigs slaughtered nationally according to weight (50-110 kg and >110 kg) Annual number of pigs exported live from Denmark according to age group (weaners (15-50 kg), finishers and sows)

3.3 Study 3: consequences on health and productivity following introduction of the yellow card initiative (paper III)

The third study (paper III) investigated, whether the rapid decrease in antimicrobial consumption following introduction of the yellow card initiative had affected pig productivity and health, measured as mortality, daily weight gain, lean meat percent and lesions at slaughter, and how the reduction in antimicrobial consumption had been achieved according to veterinarians and farmers. The study was performed as a retrospective, observational study based on information from interviews, questionnaires, databases (VetStat and CHR), herd production reports and abattoir data. Results on antimicrobial consumption were based on a VetStat data withdrawal performed 16 April 2014. For each productivity and health variable, the year prior to introduction of the yellow card initiative (1 June 2009 – 31 May 2010) was compared to the year after introduction of the yellow card initiative (1 June 2010 – 31 May 2011). Results are presented in paper III.

3.3.1 Herd selection and data collection

Initially, 650 herds were randomly selected among all Danish pig herds with a $\geq 10\%$ reduction in antimicrobial consumption following the introduction of the yellow card initiative and ≥ 500 pigs registered in the corresponding age group. Herds were then evaluated for inclusion and exclusion criteria based on database information from VetStat and CHR and through a telephone interview. Herds were excluded, if they had undergone any major changes during the study period, such as change in owner, abattoir, veterinarian or performed an eradication program. The telephone interview was performed by the interviewer reading aloud from a questionnaire to ensure identical wording. Included herds were then asked (i) to answer a questionnaire on how the reduction in antimicrobial consumption had been achieved; (ii) to submit production data on mortality and daily weight gain; and (iii) if the herd had decreased finisher antimicrobial usage, to submit a written signature allowing access to abattoir data. An overview of the collected information is shown in Appendix III. All questionnaires are shown in Appendix IV.

Changes in average mortality and daily weight gain were analysed with a pairwise t-test. Standard deviation of the daily weight gain was analysed with a repeated measurements analysis of variance and changes in lean meat percent and lesions at slaughter were analyzed with generalized linear mixed models.

3.3.2 Overview of model variables

Analysis of changes in daily weight gain

Daily weight gain standard deviation was calculated for each period at herd level. This was done by first calculating the standard deviation of all values on daily weight gain submitted for the corresponding period separately for each herd. This resulted in two numbers for each

herd, one on the standard deviation of daily weight gain in the first period and one for the second period. These two numbers were then investigated in the model. All variables included in the initial model are shown in Table 3.2.

Table 3.2. Variables included in the repeated measurements analysis of variance when evaluating change in daily weight gain standard deviation.

Dependent variable	Level	Variable classification	Variable description
Daily weight gain standard deviation (log-transformed)	Herd	Quantitative, continuous	Standard deviation of daily weight gain-measurements according to herd production reports in period 1 and period 2, respectively,
Independent variables			
Herd (random effect)	Herd	Qualitative, nominal	Herd identification code as according to the Central Husbandry Register
Period	Herd	Qualitative, nominal	The year before (1 June 2009-31 May 2010) or the year after the introduction of the yellow card initiative (1 June 2010-31 May 2011)

Analyses of changes in lean meat percent and lesions at slaughter

Abattoir data was stated for each individual pig, including information on date received at abattoir, herd from which the pig had been received, lean meat percent and whether any lesions was found on the pig. If a lesion was found, then the type of lesion was stated in the pig's abattoir data entry.

All variables included in the initial generalized linear mixed models are shown in Table 3.3. See paper III for a table overview of the full models (paper III, Table 2).

Table 3.3. Variables included in the generalized linear mixed model applied when evaluating (i) change in lean meat percent, (ii) lean meat percent standard deviation, and (iii) prevalence in lesions at slaughter.

Dependent variables	Level	Variable classification	Variable description
Lean meat percent (i)	Pig	Quantitative, pseudo-continuous	Lean meat percent at slaughter
Lean meat percent standard deviation (ii)	Batch	Quantitative, pseudo-continuous	Standard deviation of lean meat percent at individual batch level
Diseased (iii)	Pig	Qualitative, dichotomous	Lesion at slaughter: yes/no
Independent variables			
Batch	Batch	Qualitative, nominal	Groups of pigs received at the abattoir on the same date from the same herd
Herd	Herd	Qualitative, nominal	Group of pigs received at the abattoir from the same herd
Period	Batch	Qualitative, nominal	The year before (1 June 2009-31May 2010) or the year after the introduction of the yellow card initiative (1 June 2010-31May 2011)
Season	Batch	Qualitative, nominal	Winter, Spring, Summer, Autumn

4 Overview of results in the PhD project

4.1 Present structure of Vetstat

Two peer-reviewed central papers were identified on the description of VetStat, “VETSTAT – the Danish system for surveillance of the veterinary use of drugs for production animals” by Stege et al. published in 2003 and “Veterinary antimicrobial-usage statistics based on standardized measures of dosage” by Jensen et al., published in 2004.

4.1.1 User-access to VetStat data

Numbers on national veterinary antimicrobial consumption are freely available online on DVFA’s website, presented both as an overall number and for pigs separately (Danish Veterinary and Food Administration, 2016).

VetStat has its own website, <https://vetstat.dk>. To obtain access to the website, a username and password must be obtained through DVFA. Prior to spring 2012, only farmers and veterinarians had access to the website, allowing them access to all entries pertaining to their own affiliated herds. On the website, automated graphic reports can be accessed showing each individual herd’s antimicrobial consumption in ADD per 100 animals per day, both as the monthly average and as a nine month rolling average. In November 2011, the Danish Parliamentary Ombudsman released a decision that VetStat data should be accessible to the public upon request (the Danish Parliamentary Ombudsman, 2011). Since spring 2012, it has been possible for any member of the public to obtain access to detailed data excerpts from Vetstat and a username and password to the VetStat website upon request.

4.1.2 Submission of data into VetStat

All Danish pharmacies have since the 1980s employed a standardized IT-based reporting system, reporting all purchases of drugs to the Danish Health and Medicines Authority. With the implementation of VetStat, this system was set up to transfer data on veterinary medicine sales from the Danish Health and Medicines Authority onwards to VetStat. The link ensures automatic transfer of data on all veterinary drug purchases (Jensen et al., 2004).

Electronic journal systems are used by most Danish veterinary practices. These software-systems automatically transfer data on all treatments regarding production animals to Vetstat as part of their billing functionality (Jensen et al., 2004). The software-systems are developed

and distributed by private companies. The configurations of these software-systems are not subject to any official guidelines or legislations. A few veterinarians choose to report data directly into Vetstat, either manually on the Vetstat website or by discs sent to DVFA. According to Danish legislation veterinarians must report drugs used for production animals at least once per month (Anonymous, 2015b).

Only a few substances are approved for pre-mixed medicated feed for production animals. The purchases are reported directly to Vetstat by the feed-mills (Jensen et al., 2004).

4.1.3 Data validity in VetStat

During the first years following the implementation of VetStat in 2000, various types of errors were still frequently discovered. In 2001, 6-7% of sales registrations by pharmacies were rejected in VetStat, the majority due to errors in product numbers (Stege et al., 2003). In 2004, data completeness had reportedly increased for pharmacies and feed mills to a 99% coverage (Jensen et al., 2004). However, up until 2005 delays in data transferral of up to three months still occurred between actual purchase at the pharmacy and registration in VetStat (Ministry of Food, Agriculture and Fisheries, 2008). Despite the reported increase in pharmacy and feed mill data completeness, usefulness and validity of VetStat data were questioned as late as 2007, due to the continuing occurrence of errors in pharmacy registrations, such as erroneously stated disease group or wrong herd identification number (Strunz and Pedersen, 2007). Furthermore, in 2014 an internal instruction guide for DVFA employees was released, which reported that mistakes in the registration of age group still occurred (Danish Veterinary and Food Administration, 2014). This type of error where an entry contains a wrong yet valid age group, e.g. a VetStat entry stating that a product had been sold for use in weaners despite the herd not having any weaners, received special attention in relation to the release of the yellow card initiative. Prior to the actual instigation of the yellow card initiative, warning letters had been dispatched to farmers, who according to Vetstat and CHR data had an antimicrobial consumption close to or above the then set threshold value, calculated as number of ADDs/100 animals/day (Andreasen et al., 2012). Here, instances of discrepancies were discovered between (i) the actual number of animals in the herd and the number of animals registered in CHR; and (ii) the age group stated on the veterinarian's prescription and the age group registered in VetStat as receiving the medicine. If e.g. a herd had no weaners registered in CHR, but a pharmacy by mistake registered a sale of antimicrobials for use in weaners, the herd in question would receive an antimicrobial consumption report stating that the herd had treated 100% of their weaners per day in the corresponding time period. To avoid penalizing farmers erroneously, the farmer has, since the introduction of the legislation, had the opportunity to raise objections to DVFA upon receiving a yellow card penalty, if he or she believes the yellow card is wrongfully designated (Danish Veterinary and Food Administration, 2014).

With regards to data registered by veterinary practitioners, it was in 2005 still estimated that 20% of the antimicrobials used in veterinary practice were not registered in to VetStat (DANMAP, 2005). However, from 2010 to 2012 it was estimated that 10% of the antimicro-

bials used in veterinary cattle practice were not registered into Vetstat by the veterinary practitioners (DANMAP, 2012b). According to the DANMAP 2011 report, about half of the antimicrobials sold for use in cattle were purchased through veterinary practitioners in 2011 (DANMAP, 2011). Additionally, the DANMAP 2011 report states that the data quality of entries pertaining to antimicrobials sold for use in pigs registered by veterinary practitioners was not at an acceptable level prior to 2005 (DANMAP, 2011).

4.1.4 Effect of calculation routines on cattle antimicrobial consumption reports

Numbers on the Danish cattle antimicrobial consumption are published yearly in the annual DANMAP reports (DANMAP, 2011). To adjust for potentially missing registrations by veterinary practitioners, DANMAP has previously validated the amount of antimicrobials registered by veterinary practitioners with the amount of antimicrobials sold by the pharmacies for use in cattle practice. This can be calculated as:

$$\begin{aligned} & \text{DANMAP cattle antimicrobial quantity} \\ &= \text{antimicrobials sold directly for use in cattle herds from pharmacies} \\ &+ \text{antimicrobials sold for use in cattle practice from pharmacies} \end{aligned}$$

(DANMAP, 2010)

By applying this method, antimicrobial consumption can be estimated solely on data registered by pharmacies. However, registrations by pharmacies on antimicrobials sold for use in veterinary practice do not include information on animal species. Therefore, this method may be especially vulnerable as it is based on the assumptions that (i) all antimicrobials sold for use in cattle practice are used in cattle and that (ii) only antimicrobials purchased directly from the pharmacies or sold for use in cattle practice are used in cattle. Not including antimicrobials sold for use in a mixed practice may potentially lead to an underestimation of the actual consumption, if the practice sells or uses antimicrobials for cattle. Furthermore, antimicrobials sold for use in a cattle practice, but used or sold by the veterinarian for use in another animal species may lead to an overestimation of the actual consumption.

An alternative to the DANMAP method is solely to include data where the animal species has been explicitly specified as “cattle”. This method does not adjust for missing registrations by veterinary practitioners.

Discrepancies between 4% and 15% were observed when comparing the annual estimated cattle antimicrobial consumption using the two aforementioned methods (Table 4.1).

Table 4.1. Cattle antimicrobial consumption (kg of active ingredient) from 2007 to 2011 according to (i) the DANMAP calculation method; and (ii) as registered for use in cattle in VetStat.

	Vetstat	DANMAP	Discrepancy (kg active ingredient)	Discrepancy in %
2007	12741	15000	2259	15.1
2008	12923	14500	1576	10.9
2009	13232	15000	1768	11.8
2010	14027	14636	608	4.2
2011	13671	14678	1006	6.9

This comparison highlights the importance of meticulous description of calculation routines when publishing numbers on antimicrobial consumption.

4.1.5 Illustration of the historic development in Vetstat registrations on pig antimicrobial usage

An investigation was made to determine the development over time in (i) registration of antimicrobial sales according to reporting entity (pharmacy/feed mill/veterinary practitioner); and (ii) percentage of entries concerning antimicrobials sold for use in pigs containing an invalid age group. VetStat entries on antimicrobials sold for use in pig herds from 2002 to 2013 were investigated. Since 2002, pharmacies have registered the majority of antimicrobials sold for use in pigs, accounting for 97.7% in 2002 and steadily increasing since then. As a result, 99.9% of the pig antimicrobial consumption were registered by pharmacies in 2013. For all investigated years, veterinary practitioners registered less than 2%, accounting for 0.1% in 2013 (Table 4.2).

The share of entries containing an invalid age group has been steadily decreasing, from 1.5% in 2002 to 0.01% in 2013. The largest decrease within a two year period was seen from 2010 to 2011 (Table 4.3). This may be related to the implementation of with the yellow card initiative in December 2010.

Table 4.2. Antimicrobials sold for use in pigs according to recording entity – 2002 to 2013.

Year	Reporting entity						Total kg active ingredient
	pharmacy		feed mill		veterinary practitioner		
	Kg active ingredient	%	Kg active ingredient	%	Kg active ingredient	%	
2002	70559	97.7	1366	1.9	297.7	0.4	72223
2003	78202	97.9	885	1.1	819.2	1.0	79906
2004	88995	97.7	855	0.9	1276.4	1.4	91127
2005	88521	97.7	837	0.9	1239.5	1.4	90598
2006	87723	98.6	428	0.5	839.9	0.9	88991
2007	93734	98.4	544	0.6	944.8	1.0	95223
2008	92752	99.6	147	0.2	207.1	0.2	93106
2009	104307	99.7	109	0.1	175.5	0.2	104592
2010	101064	99.8	36	0.0	121.9	0.1	101222
2011	81888	99.8	43	0.1	87.7	0.1	82018
2012	74070	99.7	85	0.1	105.5	0.1	74261
2013	90853	99.9	5	0.0	114.3	0.1	90972

Table 4.3. Antimicrobials sold for use in pigs according to registered age group – 2002 to 2013.

Year	Pre-weaning pigs and breeding animals		weaners		finishers		invalid age group		Total kg active ingredient
	Kg active ingredient	%	Kg active ingredient	%	Kg active ingredient	%	Kg active ingredient	%	
2002	20800	28.8	28489	39.4	521867	30.3	1067.2	1.5	72222.9
2003	23387	29.3	29094	36.4	126146	32.7	1278.7	1.6	79906.0
2004	24706	27.1	34222	37.5	530214	33.2	1984.4	2.2	91127.0
2005	24647	27.2	33923	37.4	430439	33.6	1588.7	1.8	90597.7
2006	24237	27.2	33831	38.0	229387	33.0	1535.3	1.7	88991.1
2007	28087	29.5	36465	38.2	29635	31.1	1035.5	1.1	95223.0
2008	28116	30.2	35741	38.3	28533	30.6	715.7	0.8	93105.9
2009	31306	29.9	41231	39.4	231527	30.1	528.6	0.5	104592.3
2010	30046	29.7	38968	38.5	31979	31.6	228.1	0.2	101222.0
2011	23844	29.1	32057	39.0	26101	31.8	16.9	0.0	282018.4
2012	23941	32.2	23913	32.2	206397	35.5	9.5	0.0	174260.8
2013	25017	27.5	38055	41.8	327892	30.7	8.4	0.0	190971.6

4.2 Paper I

To address the challenges encountered when estimating actual herd antimicrobial usage based on VetStat data, a total of ten interinstitutional panel group meetings were held. Eleven key challenges were identified, described and corresponding solutions were compiled and discussed. The identified challenges could be divided into two main categories: (i) challenges arising due to data quality and system structure; and (ii) challenges arising during actual calculation of antimicrobial usage and data handling. Essentially, all major challenges could be attributed to the difficulties encountered when attempting to transform secondary sales data into an estimation of true exposure. The importance of each challenge was found to be highly contingent on the research question. No specific challenge could therefore be put forward as that of most importance. The findings of this study underline the importance of cleaning, checking and validating data prior to use, a statement which is true for any dataset regardless of origin (Emanuelson and Egenvall, 2014) and in particular when using secondary data (Arnold et al., 1999; Ogdie et al., 2012).

4.3 Paper II

The study was conducted as a retrospective, observational database study with the aim to (i) describe the previous and present methods used by two major Danish institutions to assign ADD-values; and (ii) illustrate how differences in choice of population and assigned ADD-values affect the calculated national pig antimicrobial consumption in the years surrounding the introduction of the Yellow Card initiative (2007-2013).

ADD was defined as the assumed average maintenance dose per day for the main indication in a specified species (Jensen et al., 2004). The three major sets of ADD-values applied when calculating Danish pig antimicrobial consumption were evaluated for differences. The VetStat ADD-values differed from the DVFA and DANMAP ADD-values by being founded on dosages stated in each product's Summary of Product Characteristics, whereas both DVFA's and DANMAP's ADD-values were based on the individual product's active ingredient(s), concentration and administration route (DANMAP, 2012a; Anonymous, 2014a). However, despite seemingly identical theoretical foundations, DVFA and DANMAP ADD-values were only identical for 48% of their common 648 antimicrobial products.

National pig antimicrobial consumption was calculated as number of ADDs/pig/year for the period 1 January 2007 to 31 December 2013. Calculated results and trends over time were found to vary greatly depending on chosen set of ADD-values and population measurement. When calculated as number of ADDs/pig/year using either pigs slaughtered per year or pigs according to Statistics Denmark as population measurement and DVFA ADD-values, the antimicrobial consumption was found to have increased by 22% from 2007 to 2013. However, performing the same calculation with pigs produced per year (slaughtered nationally + live

export) as population measurement and the VetStat ADD-values, the consumption from 2007 to 2013 was found to have decreased by 11%.

4.4 Paper III

Study 3 was conducted as a retrospective observational study investigating (i) how the antimicrobial consumption had been reduced following the introduction of the yellow card initiative; and (ii) whether the reduction in antimicrobial consumption had affected productivity and health in weaners and finishers.

Of the 650 initially selected study herds, 52% were excluded (339/650 herds). For 8.3% of the herds either the veterinarian or farmer did not wish to participate at all (54/650 herds). Of the remaining 257 herds which were all included, 202 herds submitted a questionnaire on how the reduction in antimicrobial consumption had been achieved. In total, 58 veterinary practitioners responded to a similar questionnaire. Increased use of vaccines (51.5% of farmers and 35.0% of the veterinarians), less herd medication (44.1% of the farmers and 57.9% of the veterinarians) and staff education (19.8% of the farmers and 25.0% of the veterinarians) were the most frequent factors stated to have contributed to the decrease in antimicrobial usage. However, shorter treatments (16.8% of farmers and 15.0% of the veterinarians) and smaller dosages of product (14.4% of farmers and 4.3% of the veterinarians) were also stated by some. In general herd managers and veterinarians had very poor agreement, except for increased use of vaccines, where a fair agreement was observed (evaluated with a simple Kappa statistic).

Data on mortality were obtained from 49 weaner herds and 38 finisher herds. Data on daily weight gain were obtained from 43 weaner herds and 38 finisher herds. Data on lean meat percent and lesions at slaughter were collected for 75 herds (841,948 pigs in total). For weaners, a significant increase in mortality was observed from 2.4% to 3.1% ($p=0.0001$). For daily weight gain, a trend was observed towards a lower average (447 to 436 grams/day; $p=0.12$) and a higher standard deviation (43.2 to 48.1; $p=0.56$). Weaner herds with a high initial antimicrobial usage ≥ 25 ADDs/100 pigs/day had a significantly higher increase in mortality compared to herds with a lower initial antimicrobial consumption ($p=0.02$).

For finishers, trends were observed towards a higher mortality (3.3% to 3.7%; $p=0.51$), a lower average daily weight gain (890 to 867 grams per day; $p=0.71$) and a higher daily weight gain standard deviation (58.8 to 64.0; $p=0.43$).

Lean meat percent at slaughter increased significantly from 60.05 to 60.18 ($p<0.0001$). However, the lean meat percent standard deviation decreased slightly during the same period (4.4 to 4.2; $p=0.64$). The prevalence of 13 types of lesions at slaughter were investigated before and after the introduction of the yellow card initiative. Significant increases in localized tail bites (OR= 1.8), chronic peritonitis (OR= 1.3) and abscesses in heads and ears (OR= 1.2)

were observed ($p < 0.0001$). Chronic pleuritis (OR= 0.9), abscesses in front- mid- and rear section (OR= 0.84), chronic pneumonia (OR= 0.8), abscesses in feet and legs (OR= 0.7) and infected tail bites (OR= 0.4) all decreased significantly ($p < 0.0001$). The prevalence of osteomyelitis, chronic enteritis and chronic infectious arthritis did not change significantly. Chronic pleuritis had the highest herd median odds ratio (MOR) at 19.9 and infected tail bites the highest batch MOR at 2.03.

5 Papers

5.1 Paper I

Improving institutional memory on challenges and methods for estimation of pig herd antimicrobial exposure based on data from the *Danish Veterinary Medicines Statistics Program (VetStat)*.

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Improving institutional memory on challenges and methods for estimation of pig herd antimicrobial exposure based on data from the Danish Veterinary Medicines Statistics Program (VetStat).

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Abstract

With the increasing occurrence of antimicrobial resistant human pathogens, more attention has been directed towards surveillance of both human and veterinary antimicrobial use. Since the early 2000s, several research papers on Danish pig antimicrobial usage have been published based on data from the Danish Veterinary Medicines Statistics Program (VetStat). VetStat was formed in 2000 and functions as a national database containing detailed information on purchases of veterinary medicine. This paper describes a selected set of challenges encountered when attempting to assess actual antimicrobial exposure at herd level based on VetStat data and suggests corresponding solutions. Challenges and solutions presented were elected based on consensus of an interinstitutional researcher collaboration. Focus is placed on establishing uniform methods of extracting and editing data in order to obtain reliable estimates of antimicrobial consumption at herd level in the pig production. This was done to aid researchers new to VetStat data, improve institutional memory and provide useful information to other countries considering the construction of similar databases on veterinary drug use.

Keywords

VetStat, antimicrobial exposure estimation, national databases, antibiotic use, swine, data management

Abbreviations

ADD: Animal Defined Daily Dose

ADDs: Animal Defined Daily Doses

ATC: Anatomical Therapeutical Chemical

CHR: Central Husbandry Register

DANMAP: The Danish programme for surveillance of antimicrobial consumption and resistance in bacteria from animals, food and humans

DVFA: The Danish Veterinary and Food Administration

Introduction

During the last two decades, antimicrobial resistance and responsible use of antimicrobials have become subjects of growing interest in the Public Health community. In the European Union alone, it is estimated that infections caused by antimicrobial-resistant bacteria are responsible for at least 25,000 human deaths per annum in addition to a societal cost of 1.5 billion Euros

per year (McEwen and Fedorka-Cray, 2002; European Centre for Disease Prevention and Control, 2009; European Medicines Agency, 2011). These figures are largely perceived as a consequence of imprudent antimicrobial use in both humans and animals (Laxminarayan et al., 2013; Hammerum et al., 2014). One of the key elements in understanding development of antimicrobial resistance is a detailed knowledge of actual antimicrobial usage.

This has led international institutions, such as the World Health Organization and the European Council, to recommend increased surveillance of antimicrobial usage (European Medicines Agency, 2011; World Health Organization, 2015).

In Denmark, detailed data on all purchase of veterinary medicine have been collected since 2000 in the Danish Veterinary Medicines Statistics Program (VetStat). VetStat was originally designed with four aims: *“(1) to monitor veterinary usage of drugs in animal production; (2) to help practitioners in their work as herd advisors; (3) to provide transparency as a basis for ensuring compliance with rules and legislation and (4) to provide data for pharmaco-epidemiological research”* (Stege et al., 2003). While aims (1) to (3) have aided risk managers in decision-making processes and ensured compliance with legislative initiatives (Jensen et al., 2004; Aarestrup et al., 2010; Jensen et al., 2014), aim number (4) has been the one to attract most interest from the scientific community. For researchers, VetStat data represent a valuable data source, containing detailed information on all purchases of veterinary medicine in Denmark. It is therefore tempting to use VetStat data as a proxy when estimating antimicrobial exposure, as it: (i) requires no field work and is consequently cheaper than collecting primary data; (ii) is the closest secondary information to data on actual antimicrobial usage; (iii) has national coverage and includes all Danish herds with production animals receiving prescription-only drugs; and (iv) stores data over time, allowing for retrospective, longitudinal studies to be performed. Consequently, VetStat data have been used in several studies and reports describing and investigating the antimicrobial consump-

tion in Danish pigs (Emborg et al., 2007; Vieira et al., 2009; Hybschmann et al., 2011; DANMAP, 2014; Fertner et al., 2015a). However, as VetStat data are purchase data and not actual consumption data, discrepancies between registrations in VetStat and actual usage after purchase may exist. Consequently, it is necessary to understand and address such discrepancies before attempting to interpret approximations on antimicrobial exposure based on VetStat data. In this paper, the issues encountered when attempting to address presented discrepancies are referred to as “challenges”, as they do not necessarily imply errors in data or lack of data quality, but may originate from this discrepancy between purchase and actual consumption.

Previous papers have in detail described the structure of the VetStat database and the most frequent calculation routines applied when reporting antimicrobial consumption based on VetStat data (Stege et al., 2003; Jensen et al., 2004). However, to the authors’ knowledge no publication has yet addressed challenges encountered when using VetStat data to estimate antimicrobial exposure in pigs at herd level or the following implemented solutions. Importantly, some challenges and the corresponding solutions may be less evident for researchers who have not worked intimately with VetStat data before. Non-awareness of presented challenges may introduce a potential risk of misinterpretation of results and a lack of knowledge on potential solutions an increased risk of erroneous corrections. Hence, it was decided to contribute to institutional memory in the anticipation that this will facilitate the use of VetStat data in future scientific studies. Furthermore, the challenges and solutions ad-

dressed in this paper may also provide useful information to other countries considering constructions of similar databases on veterinary drug use.

Objective

This paper aims at improving institutional memory and aiding people using VetStat for research purposes by establishing uniform methods of extracting and editing data in order to obtain reliable estimates on pig antimicrobial consumption at herd level. The objective is therefore to present a critical set of challenges encountered when using VetStat data to estimate antimicrobial exposure in Danish pig herds and offer at least one robust solution for each challenge presented.

Materials and methods

VetStat

VetStat is a national database containing detailed data on all purchases of prescription-only drugs for use in production animals. It is constructed as a relational database (Figure 1) on an Oracle platform and is presently owned and managed by the Danish Veterinary and Food Administration (DVFA), a sub-department under the Ministry of Environment and Food of Denmark. In Denmark, antimicrobials for veterinary use can only be purchased with a valid prescription from a veterinarian (Anonymous, 2015). Therefore, all purchases of antimicrobials are recorded in VetStat. Sales of veterinary antimicrobials happen through pharmacies, veterinary practitioners and feed mills (Stege et al., 2003).

Each VetStat data entry contains information on date of purchase, product identification code, amount of product purchased, identification code of the reporting pharmacy, veterinarian or feed mill, identification code of prescribing veterinarian, herd identification code and which age and disease group the product was prescribed for (Jensen et al., 2004). Pigs are divided into three age groups with corresponding standard weights: (i) pre-weaning pigs, sows, boars and bred gilts (200 kg), (ii) weaners (15 kg) and (iii) finishers and un-bred gilts (50 kg). Six disease groups (indications) for pigs exist: (1) reproduction and urogenital system, (2) udder, (3) gastrointestinal system, (4) respiratory system, (5) joints, limbs, hooves, skin and central nervous system and (6) metabolism, digestion and circulation (Stege et al., 2003).

Within the VetStat database environment, purchase data registered by pharmacies, veterinarians and feed mills can be supplemented with information from additional tables, such as product trade names, concentrations, active ingredients, administration routes and dosages per kilogram of live animal (Figure 1). In 2015, 99.8% of antimicrobials purchased for use in pigs were registered by the pharmacies (E. Jacobsen, personal communication). It is therefore reasonable to assume that in the majority of studies, a solid exposure dataset can be obtained solely from pharmacy records. For that reason, this paper only includes challenges encountered when using data registered by pharmacies. A complete overview of the relevant VetStat tables used to estimate antimicrobial pig exposure based on pharmacy registrations is shown in both Figure 1 and Appendix 1.

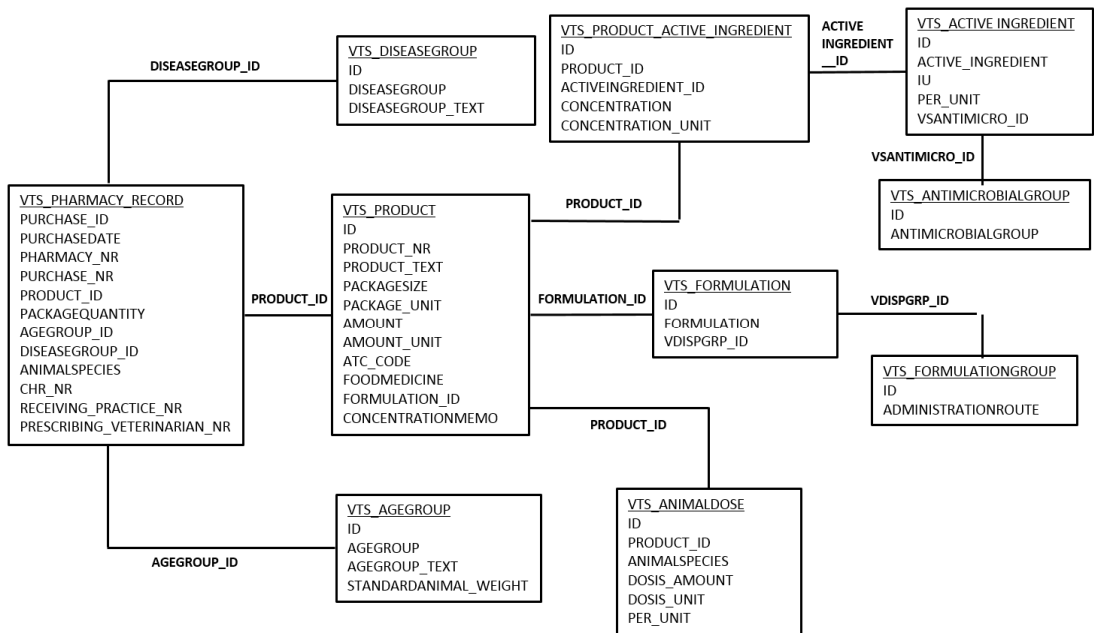


Figure 1. Overview of selected antimicrobial related VetStat tables, their connections and chosen variables. Detailed descriptions of each variable are shown in Appendix 1.

The Central Husbandry Register

In order to standardize treatment exposure at herd level, the number of pigs present must also be known at herd level. In Denmark, the Central Husbandry Register (CHR) is the central database used for registration of holdings and animals. It was established in 1992 and is owned by the Ministry of Environment and Food of Denmark. Among other herd level information, CHR holds data on number of pigs according to age group (Anonymous, 2014). For identification, each herd is assigned a unique identification number based on geographical location, known as the herd's CHR number. As in VetStat, pigs in CHR are divided into three age groups: weaners (7-30 kg), finishers (30 kg-slaughter) and breeding animal (200 kg). For all practical purposes, these corre-

spond to the age groups used in VetStat, defining weaners as 7-30 kg pigs with a 15 kg standard weight (from VetStat), finishers as pigs in the interval from 30 kg to slaughter with a standard weight of 50 kg (from VetStat) and breeding animals with a standard weight of 200 kg (from VetStat). The number of animals must be updated twice per year for larger pig herds (>300 sows, >6000 weaners or >3000 finishers) and once per year for smaller herds (Anonymous, 2013).

Estimating antimicrobial exposure

Antimicrobial exposure calculated based on secondary data can e.g. be reported as "kilogram of active ingredient" or "Animal Defined Daily Doses" (ADDs). In VetStat, those measures are calculated as:

$$\text{kilogram of active ingredient} = \frac{\text{quantity of purchased product} * \text{concentration} \left(\frac{\text{mg}}{\text{unit}}\right)}{1000000}$$

Formula 1. Calculation of kilogram of active ingredient based on values in VetStat

$$\text{ADD} = \frac{\text{quantity of purchased product}}{\text{dosage per kg live weight} * \text{standard weight of corresponding age group}}$$

Formula 2. Calculation of Animal Defined Daily Doses (ADD) based on standardized VetStat values on dosage per kg live weight and animal standard weights.

One Animal Defined Daily Dose (ADD) has been defined as “*the assumed average maintenance dose per day for the main indication in a specified species*” (Jensen et al., 2004; DANMAP, 2009).

Presently three different datasets on standard dosages exist: (i) the animal equivalency dataset used by the Danish Veterinary and Food Administration (DVFA) prior to the 30th of November 2014 in connection to the Yellow Card legislation (Jensen et al., 2014); (ii) the animal equivalency dataset used by DVFA following the 30th of November 2014; and (iii) the animal equivalency dataset first used in the 2012 report from the Danish programme for surveillance of antimicrobial consumption and resistance in bacteria from animals, food and humans (DANMAP) (DANMAP, 2012). At present, only the second dataset is available through ordinary VetStat data withdrawals. However, this may change over time. Researchers are recommended

to obtain up-to-date knowledge before deciding which animal equivalency dataset to use when estimating antimicrobial exposure in ADDs. Differences among the three equivalency datasets were described in a paper by Dupont et al. in 2014 (Dupont et al., 2014) and related advantages and disadvantages of the various types of calculation are beyond the scope of this paper.

Presenting challenges and solutions

Three main types of challenges are presented in this paper. The three types of challenges relate to: (i) data quality and the system structure; (ii) estimating exposure based on purchase data and (iii) calculation of ADDs and data handling. Figure 2 illustrates differences between information available in VetStat and information required for antimicrobial exposure estimations. In the Results section, each challenge is presented followed by one or more sug-

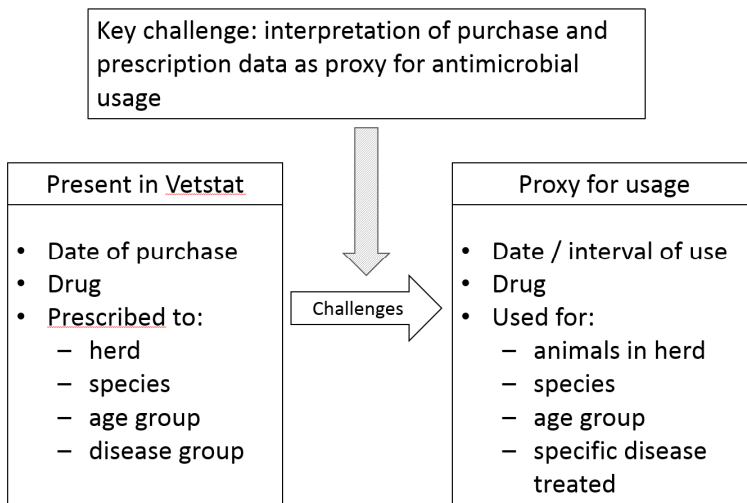


Figure 2. Graphical illustration of the key challenge encountered when using VetStat data for research on antimicrobial exposure in pigs.

gested solutions. Issues and limitations of the suggested data management procedures are covered in the discussion.

The relevance of each challenge will, to a large degree, depend on the study objective and methods used. The focus of the present study was therefore not on performing a specific detection of data inconsistencies or a quantitative data quality evaluation. Consequently, it was considered unnecessary to show any numbers from specific data extractions, as the frequency of errors and inconsistencies found in a dataset will vary, depending on the period covered or when the dataset was extracted. Additionally, the observed percentage of a given error may not necessarily reflect its true impact on exposure estimation.

The present paper was developed by an interinstitutional panel of PhD students from the National Veterinary Institute, National Food Institute and the University of Copenhagen; under the supervision of an Assistant Professor from the National Food Institute. All members of the panel had between two and five years of experience with VetStat data through involvement with previous research or advisory service. In addition, two members also had previous experience as veterinarians in Danish swine production farms. Consensus on challenges and solutions was developed through a series of ten discussion meetings, which took place during the length of two years, allowing for a systematic analysis of the steps needed to obtain robust exposure information when using VetStat purchase data. When necessary, further support and information was sought from DVFA employees maintaining or utilizing VetStat. This was done to assure consistency with

the system's official descriptions and working procedures.

Results

Data quality and system structure

Challenge 1: Lack of consistency between datasets extracted at different time points

Data submitted by the pharmacies are uploaded to VetStat continuously. Extractions for a specific time period may therefore contain different data, if (i) a dataset is extracted right before or after a VetStat data update; (ii) a transfer fail occurs while extracting data from VetStat to a local computer; or (iii) manual corrections to single entries are performed by DFVA employees (E. Jacobsen, personal communication). No logs on such manual corrections are presently publicly available and previously extracted datasets may therefore be non-reproducible.

Solution: Data should be checked for integrity of records. One indication of integrity is the presence of records in all months. Another way to validate an extracted dataset is to compare the total amount of purchased antimicrobials in the dataset (in kg of active ingredient) with the numbers published on the DVFA website (Danish Veterinary and Food Administration, 2016). Completeness of data can also be double-checked by comparing the number of records in randomly selected periods with an additional extraction, if one is available. If data used in a specific study seem completely at odds with data from similar populations or findings published in previous papers or reports, an attempt can be made to obtain permission to contact the specific pharmacy, prescribing veteri-

narian or herd for an in-depth trace back of information. This solution can be very time-consuming and relies on the feasibility of contacting the relevant parties, which may require additional permissions. Once a valid dataset is obtained, any further manual corrections should be written in a detailed log, together with the original date and time of extraction, to ensure the maximal degree of transparency and reproducibility possible.

Challenge 2: Incorrect values in supplementary data

As previously mentioned, VetStat contains several types of tables. Besides from the tables containing purchase data registered by the pharmacies, veterinarians and feed mills, VetStat also contains tables only listing supplementary information, such as trade names, concentrations, package sizes, active ingredients, dosage per kg live weight animal and administration routes (Figure 1, Appendix 1). These are manually entered into VetStat by DVFA employees. Typing errors in supplementary data are not very frequent and are corrected as soon as they are detected (E. Jacobsen, personal communication), but have the potential to affect multiple registrations, also far back in time, from the day they occur.

Solution: Errors in supplementary data are not easily detected. However, if seemingly odd values, e.g. if a product's value for dosage per kg live weight animal is highly at odds with similar products, DVFA employees can be contacted to confirm or disprove the value in question.

Challenge 3: Prescriptions divided into more than one entry

Almost identical entries may occur in a dataset, where only identification number of the individual sale and potentially, the number of packages sold differ. This occurs when (i) packages sold originate from two different batches of drugs, as the batch number must be recorded for future reference; (ii) packages of the same product were prescribed for treatment of different diseases within the same VetStat disease group (e.g. arthritis and meningitis); or (iii) packages of the same product were prescribed for different types of pigs within the same age group (e.g. treatment of tail bites in both unbred gilts and finishers). Information on product batch number is only available at the pharmacies. No information on product batch number is sent to VetStat.

Solution: Users should be aware of split prescriptions when investigated hypotheses include antimicrobial exposure assessment based on number of prescriptions or aims at investigating prescribing behaviour in veterinarians. Identical entries should be considered as one, if deemed to have been split due to different batch numbers. For entries split due to age or disease grouping (VetStat disease group versus individual diseases), the individual study's objective should determine, if split entries should be merged or counted separately.

Challenge 4: Negative entries

Return of unused drugs and corrections of errors in original registration result in VetStat entries with a negative amount of packages purchased. This poses a challenge for researchers summarizing data with time

as a grouping variable, since negative entries can be registered in VetStat at any time following the original sale. Often these type of entries will be on the same calendar date. According to DVFA working procedures, a negative entry may only be made by the pharmacy, if the corresponding positive entry is within the same calendar month. If corrections need to be made at a later time, they must be carried out by DVFA employees. However, several instances occur where there is a seemingly longer time interval between the negative entry and its corresponding positive entry. If the original sale and the corresponding correction are located in different time-slices, the lag time between the two will result in an overestimation of consumption at the time of purchase and a consequent underestimation at the time of correction. The risk of splitting original records from their corresponding corrections increases as time intervals summarizing the consumption become smaller, e.g. when comparing weeks or months instead of years.

Solution: Studies investigating smaller time intervals might suffer from biased estimates of antimicrobial consumption data. It is recommended to investigate a buffer period both before and after the actual study period, as it increases the chance of correctly pairing negative entries and their positive counterparts. In Denmark, the use of antimicrobials for oral medication is permissible up to a maximum of 35 days after the veterinarian has issued the prescription. For all other drugs the period expands to 63 days (purely finisher herds) or 50 days (all other herds) (Anonymous, 2015). All herds who wish to use antimicrobials for oral medication must therefore have monthly visits by a veterinarian. If

only needing injectable antimicrobials on a regular basis, this period extends to every second month. Consequently, it is sensible to include a buffer period of at least 63 days before and after the study period, as this interval corresponds to the longest period allowed between veterinary visits. Furthermore, as pharmacies transfer purchase data to VetStat at the end of each month, it is recommended to augment the buffer period by at least one month, resulting in a buffer period of at least three months before and three months after the intended study period. Negative observations and the corresponding positive purchased amounts can be matched based on prescribing veterinarian, herd, pharmacy, product, disease group and date (a retraction must necessarily occur after or on the same date as the original purchase). These should be excluded from the final dataset, as they tend to cancel each other out. However, it should be noted that the purchased and retracted amounts do not necessarily match in every case. It is recommended that positive differences are maintained and negative ones are deleted.

Assuming time slices and study populations are large enough, negative entries may not represent that large a challenge in studies which solely quantify antimicrobial consumption in kg of active ingredient or ADDs. This is because negative quantities of antimicrobials will automatically balance corresponding positive quantities, if both are present in the dataset. However, in studies investigating number of prescriptions, negative and corresponding positive entries will in most cases need to be corrected manually. Without manual correction, the pharmacy retraction will still result

in two entries, even if the quantity of purchased antimicrobials equals zero.

Challenge 5: Incorrect identification number of prescribing veterinarian

Each entry in VetStat contains a number which identifies the prescribing veterinarian. These numbers are unique identifiers assigned by DVFA to all veterinarians practicing in Denmark. The veterinarian identification numbers are mostly used when investigating veterinarian prescription patterns or impact of veterinarian on herd antimicrobial exposure. Invalid veterinarian identification numbers and valid but wrongly identified identification numbers may be present in VetStat records.

Solution: To reduce the risk of affiliating a veterinarian with a herd due to a wrongly typed veterinarian identification number, it is recommended to assign a minimum amount or percentage of entries, on which the veterinarian in question should be listed as the prescribing veterinarian for the given herd. Herd affiliation for all practicing pig veterinarians can also be obtained from Vetreg, the national veterinary registry maintained by DFVA (<http://www.vetreg.dk>).

Antimicrobial exposure estimation based on register data of purchase

Challenge 6: Incorrect animal species, age group or disease group identification code

VetStat classifies pigs according to age groups. Three valid age groups, with corresponding numbered codes, exist: 55 (pre-weaning pigs, sows, boars and gilts), 56 (weaners) and 57 (finishers). It is stated by law that one of these three approved age

groups must be specified by the veterinarian on medicine prescriptions for pigs (Anonymous, 2015) and listed in the corresponding VetStat entry. However prior to instigation of the Yellow Card legislation in 2010 (Anonymous, 2010), incidences occurred where medicine was prescribed for an invalid age group, e.g. “young pigs” (Danish Veterinary and Food Administration, 2014). Hence, the pharmacist had to make a decision on which of the three age groups, the product should be registered for in VetStat.

Mismatch between animal species, age group and/or disease group may also occur due to typing errors at the pharmacies, as the pharmacies’ interfaces are not pre-coded. This allows non-valid combinations, e.g. choosing animal species “cattle”, age group “sows” and disease group “furunculosis” (a disease code for the specific infection in fish) in the same entry.

Solution: A method to identify entries with a potentially erroneous animal species and/or age group identification code is to cross-validate the data from VetStat with CHR data. This is done by investigating whether there is a match between the population data registered in CHR and the animal species and age groups identification codes stated in the herd’s registered antimicrobial purchases. A potential lag time between actual change in types of age groups in a herd and the corresponding CHR update should be taken into consideration.

Since introduction of the yellow card legislation, veterinarians and pharmacists have become more aware of the importance of correct age group terminology and meticu-

lous typing (Danish Veterinary and Food Administration, 2014). It is therefore expected that problems regarding invalid animal species, age and/or disease group identification codes will be less prevalent in the years after the implementation of the Yellow Card legislation.

Challenge 7: Discrepancies between registered and actually treated age and disease group

Although purchase records should state the specific age group and disease group being treated, there are instances in which this is not strictly enforced. If a product, according to the herd veterinarian's guidelines, is to be used for more than one age and/or disease group, the herd manager is allowed to do so, even though the veterinarian only registers the most prevalent age and disease group in VetStat (Danish Veterinary and Food Administration, 2014). Consequently, actual treated age and disease group may sometimes deviate from what was registered in VetStat at the time of purchase.

Solution: When evaluating consumption according to age and disease group, it is important to realize that deviations between actual consumption and VetStat data may occur. Consequently, the necessary precautions should be taken prior to drawing conclusions on disease patterns based on VetStat data. For studies focusing on disease groups, the Summary of Product Characteristics (SPC) can be checked to identify if product indications stated in the SPCs match disease groups registered in the VetStat entries. Mismatches might either indicate records where "herd diagnostic prescriptions" were used, records which contain a data entry error or records where the product was prescribed for off-

label use. According to Danish legislation veterinarians are allowed to prescribe products off-label, if no alternative medicinal product is approved (Anonymous, 2015). Likewise, a product can be prescribed for an approved indication but in addition be used for another disease. Hence, this challenge is often impossible to correct for, but must be given serious consideration before drawing conclusions

Challenge 8: Time lag between date of purchase and date of use

As VetStat data are purchase data, there might be significant differences between date of purchase and date of actual usage. When performing research based on VetStat data, it may be assumed that an amount of a specific product is used in the interval between its initial purchase and the subsequent purchase of an identical product. However, as the interval between sales increases, so does the uncertainty regarding perceived time of usage.

Solution: As with all other challenges, the implemented solution should be determined by the research question. Three different approaches to data handling are suggested to solve the issue of time lag. The first suggested solution is to calculate a moving average over a longer time. This solution can be applicable when investigating trends in antimicrobial consumption, but will not yield an estimate of the actual use in a specific month or period between two purchases. The second suggested solution is to smooth and aggregate data, e.g. as described by Vigre et al. in 2010 (Vigre et al., 2010). This includes calculating antimicrobial consumption between two dates of

purchase, as the amount purchased on the first date divided by number of days until the next purchase. This solution can e.g. be applicable in studies investigating levels of antimicrobial consumption over shorter time intervals such as individual weeks or months. A third option is to expand the dataset or time interval to include a longer period of time. This solution is especially applicable when investigating finisher pig herds, which tend to receive batches of pigs with up to 13 weeks apart and are expected to have a lower treatment frequency, when compared to weaners or sows herds which will often have a higher turn-over of pigs.

Calculation of Animal Daily Doses and data handling

Challenge 9: Product identification for ADD calculations

In VetStat, all pharmacological products are identified by a unique product identification number (product ID) as well as a product number. A 100 mL bottle of Penovet (300.000 IE/ml) and a 250 mL bottle of Penovet (300.000 IE/mL) will e.g. be identified by two different product IDs and product numbers. Product ID is the database identifier, which serves as connection variable between VetStat tables, while the product number is the product identifier adopted by DVFA as part of their pharmaceutical records. Product numbers are unique for active products. However, according to DVFA working procedures discontinued products may have their product numbers re-used. Working retrospectively on data covering several years, this may result in the same product number linking to two different product IDs. This challenge is particularly relevant

when calculating ADDs based on the DVFA dosages accessible at the VetStat website (<https://vetstat.dk>). Previously, ADDs were only calculated based on dosages from the VetStat equivalency dataset, using the product ID as identifier. However, when calculating ADDs using the DVFA dosages available at the VetStat website, product number is used as product identifier. When using retrospective data, this may result in wrongly applied standard dosages for products, whose product number have been re-used.

Solution: Products with identical product numbers, but different trade names and product IDs, should be identified in the VetStat product table. The corresponding products can then be identified in the standard dosage table extracted from the VetStat website and the product numbers can be manually adjusted. It is important to assure that any changes in product number are performed identically in both the table from the VetStat website and the table from the Vetstat database, so identical product numbers match completely for trade name, package size, concentration and administration route of the product in question.

Challenge 10: Doubling the purchased amount for combination products when calculating active ingredient

All active ingredients in a product are individually listed with their corresponding concentrations in the VetStat product active ingredient table. This means combination products have one record for each active ingredient. The purchased amount of a combination product consisting of two active ingredients may therefore seemingly

double, when merging purchase data from the pharmacies with the product active ingredient table, since the original purchase entry will duplicate into two nearly identical entries where only active ingredients differ. When quantifying antimicrobial purchase in kilogram of active ingredient, combination products do not give rise to concern, since the specific concentration of each ingredient is used in the formula to proportionally divide the purchased amount of product (Formula 1). However, when calculating ADDs, the doubling of entries will lead to a doubling in the amount of sold combination products, as the ADD formula uses the amount of product purchased, not the concentration of active ingredient in each product (Formula 2).

Solution: If there is a specific interest in calculating exposure to combination products, Anatomical Therapeutic Chemical (ATC) classification system codes (World Health Organization, 2011) can be used to manually create an active ingredient variable, as combination products have different ATC codes compared to products with only one active ingredient. When quantifying the antimicrobial purchase in ADDs, the row with the active ingredient with the higher concentration in the combination should be kept, discarding the rows referring to the other components and creating a variable to describe the combination. If active ingredients are to be assessed separately, it is possible to use the concentration variable to proportionally divide the purchased amount among them, so the sum of duplicated rows results in the original amount purchased.

Challenge 11: Standardize the amount of antimicrobials purchased at herd level

To allow comparison between herds, it is necessary to standardize the amount of purchased antimicrobials at herd level. Since VetStat does not include data on population size, this information must be retrieved from other sources, such as CHR. The challenge arises, when number of animals in a herd change over time. These changes are not necessarily registered instantly in CHR or researchers may only have access to a single or few data extractions on number of animals in each herd. This may result in deviations between actual herd sizes and herd sizes according to available data.

In studies which investigate consumption in different production systems, a specific type of challenge may arise when merging data from VetStat and CHR. VetStat data is registered at herd level with each entry stating CHR number of the herd purchasing the antimicrobial product. However, a herd may have different production units listed separately in the CHR database and these units may have different production systems.

Solution: Population and purchase data can be more closely aligned, if monthly extractions of VetStat and CHR are paired. This enables the use of population data for more specific time blocks, which increases the chance of detecting updates in CHR. Alternatively, annual CHR extractions can be compared to each other to identify and exclude herds with large changes in the number of registered animals. If the herd sample size is relatively small or the research project has sufficient resources, manual extractions can be made from the

VetStat website of each herd's consumption reports. These list number of animals registered in the herd per month according to CHR.

When comparing antimicrobial exposure across production systems, it is recommended to collect supplementing information on CHR numbers consisting of more than one production unit. This should be done to facilitate a more in depth selection of study herds in accordance with the specific study objectives. As a minimum safeguard CHR numbers consisting of more than one production unit can be excluded. However, the effect of excluding said herds must be evaluated prior to making any finalized conclusions, as this may highly bias results.

Discussion

Due to its wide coverage and overall data quality (Stege et al., 2003; Jensen et al., 2004) VetStat is already being widely used as a data source in research (Pedersen et al., 2007; Vigre et al., 2008; Fertner et al., 2015b) and will, due to the increased focus on antimicrobial usage in production animals, most likely continue to be used in future research projects. To aid future researchers in working with VetStat data as a proxy for Danish pigs' antimicrobial exposure, challenges commonly encountered and corresponding proposed solutions were described in this paper. Generic data challenges were mainly caused by system artefacts, such as sale retractions, typing errors or supplementary data problems. This underlines the fact that regardless of data origin, there is always a need to clean, check and validate data regardless of the study objectives (Emanuelson and Egenvall, 2014).

The key challenge when working with VetStat data is to transform register data on antimicrobial purchases into an estimation of the true exposure, occurring after the antimicrobial product was purchased. Different clinical situations require different treatment lengths and number of daily medications. Furthermore, dosages used are adjusted according to the actual live weights of the animals. When VetStat was designed, it was not deemed feasible to include all these nuances in a national database. A compromise was therefore made to only include purchase data in VetStat and divide animals and diseases into set categories. Consequently, some exposure information is lost when reality is converted into registry data. When attempting to recreate actual exposure from VetStat data, a series of assumptions must be made. Assumptions on time and method of usage will often become larger as the study's level of detail increases. As an example, it is more likely that a drug was used within a year following purchase as opposed to two weeks after the purchase. In a similar fashion, it is safer to estimate overall consumption in an entire herd compared to estimating consumption in a specific age group or to estimate national consumption as opposed to herd level consumption.

An issue not covered as a challenge in this paper was the inclusion of sows and piglets in the same age group and the impact this may have on exposure estimation, given the difference in weight between the two in addition to the large number of piglets per sow. This is an important issue, which was not addressed as no easily implemented data management solution was evident. The only trustworthy approach to obtain

sow- and piglet-specific treatments would be to obtain primary data by contacting study herds or their veterinarians.

This paper only addresses challenges encountered when working with data registered by pharmacies, as pharmacies presently report 99.8% of the Danish antimicrobial sale for pigs. Studies focusing on veterinarian clinical practices or prescription patterns may benefit from including data from the VetStat veterinarian registrations, just as studies focusing on mineral or vitamin supplementation are likely to find value in the feed mill registrations. Although some challenges presented in this paper will also find application in datasets based on veterinarian or feed mill registrations, working with these is likely to present a whole new set of unique challenges, such as large batch purchases from feed mills separated by substantial time intervals.

An optimal method for estimating life-time exposure has yet to be developed. Entries in VetStat on pig antimicrobial purchase will always refer to an entire age group in a herd, not a single animal. Consequently, information on how many treatments a single animal has received is not readily available without directly contacting the herds. A potential approach to estimating a single pig's antimicrobial exposure might be to obtain herd size information from CHR and assume that (i) all pigs in the stated age group were treated; (ii) all purchased antimicrobials were used; and (iii) CHR data are correct and updated, both in terms of herd identification and pig population. However, such assumptions should preferably be validated through interviews, collection of primary data or other auxiliary

datasets. According to a report from the Danish industry organization Danish Agriculture and Food Council, 43.3% of the Danish swine herds registered in 2014 solely had finishers (Danish Agriculture and Food Council, 2014). Naturally, pigs in these herds have to originate from other herds. Analyses should therefore be appropriately adjusted for potential movement of pigs between herds and average number of days the pigs spend in the farrowing, nursery and finishing unit. In summation, pigs may be subject to different exposure patterns during different parts of their lives and not necessarily only subject to the exposure pattern calculated for the herd which sent them to slaughter. On the other hand, it can be argued that the antimicrobial usage closest to the time of interest is likely to have the highest influence on the level of resistance, as many types of resistance reduce with time from treatment (Vieira et al., 2009), so if the sampling point in the study is at the slaughterhouse, antimicrobial treatments in the finisher herd may be of largest importance.

As previously mentioned, focus of the present study was not on detection of data inconsistencies or on performing a quantitative data quality evaluation. As described in the first challenge (*“lack of consistency between datasets extracted at different time points”*), frequency of errors and inconsistencies may vary between datasets. In addition to this, observed percentages of a given error may not necessarily reflect its true impact on exposure estimation. One product out of the 1,189 (0.08%) in the Vetstat product information table with a number that connects it to a wrong standard dosage will have no effect in a study using kg of active ingredient as exposure

unit, but will affect all results, if ADDs are used as exposure unit and the product is frequently purchased. Similarly, antimicrobial purchases for use in weaners registered for a wrong age group will affect calculations of weight-based exposure measures or age groups comparisons. But it does not matter, if the focus of the study is on an age group not affected by the typing error.

No two studies are completely identical. To decide which challenges may have implications and which of the proposed solutions are the most appropriate, researchers should always critically assess their data in relation to their objectives.

Conclusion

Although VetStat is presently the best available source for secondary data on veterinary antimicrobial consumption in Denmark, there are several steps which must be taken when converting register data into antimicrobial consumption or exposure estimates. The lack of information on actual time and usage of a purchased antimicrobial product, as well as issues relating to data quality, system structure and the calculation of dose-based exposure, may bias estimations and hence conclusions. Depending on the study of interest it is for the individual researcher to identify which challenges are of relevance, and which solutions to choose

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Appendix 1. Names and descriptions of selected VetStat tables and their variables.

Dataset		Variables		
Name	English name and description	Name	Name in English	Description(a)
VTS_APO_MED_REG	VTS_PHARMACY_RECORD Records of sales performed by pharmacies	ID	PURCHASE_ID	Unique identification number of purchase
		UDLEVERINGSDATO	PURCHASEDATE	Date in which the purchase was made.
		APOTEK_NR	PHARMACY_NR	Identification number of the pharmacy where the purchase was made.
		EKSPEDITIONS_NR	PURCHASE_NR	Number of the transaction in the pharmacy system.
		EKSPEDITIONS_TYPE	PURCHASETYPE	Originates from the pharmacy system. Marks records to be transferred to Vetstat. All values are filled as DI (large volumes sold to vets) or ID (other veterinary uses).
		VARE_ID	PRODUCT_ID	Linking variable with dataset VTS_PRODUCT. Works as unique identifier number for products.
		PAKNINGSANTAL	PACKAGEQUANTITY	Number of packages of the product being sold. Further detailing on the quantity is obtained by using variables PACKAGESIZE and AMOUNT, from dataset VTS_PRODUCT.
		ALGR_ID	AGEGROUP_ID	Linking variable with VTS_AGEGROUP.
		ORGR_ID	DISEASEGROUP_ID	Linking variable with dataset VTS_DISEASEGROUP.
		DYREART	ANIMALSPECIES	Number code of the species of the animal for which the product was prescribed.
		CHR_NR	CHR_NR	Identification number of the herd for which the product was prescribed, as found in the CHR
		MODT_PRAKSISNR	RECEIVING_PRACTICE_NR	When a product is sold to a veterinarian for in situ use, this variable is filled in place of the herd number, otherwise it is left blank.
		RECEPT_UDST_AUT_NR	PRESCRIBING_VETERINARIAN_NR	Unique identifier of a veterinarian assigned by DVFA.
		KORREKTIONSCODE	ASK ERIK	Not in use by Vetstat. Used by the pharmacy to assign corrections to entries.
FVREG_ID	FVREG_ID	Not in use. Originally referred to DVFA Regions.		

VTS_ORDINATIONSGRUPPE	VTS_DISEASEGROUP Diagnostic group of the disease for which the drug has been prescribed	ORDINATIONSTEKST	DISEASEGROUP_TEXT	Diagnostic group in text. Describes the functional system for which the drug is being prescribed. E.g. "respiratory tract disorders" or "urogenital and reproductive tract disorders".
		ORDINATIONSGRUPPE	DISEASEGROUP	Diagnostic group coded as numbers.
		DWORDINATIONSGRUPPE	DWDISEASEGROUP	Alphanumeric field with the diagnostic groups' textual description and number codes merged together.
VTS_ALDERSGRUPPE	VTS_AGEGROUP Age groups or production categories of the animals for which the drug has been prescribed	ALDERSGRUPPE	AGEGROUP	Animal age groups coded as numbers. E.g. 55 for sows/piglets, 56 for weaners, 57 for slaughter pigs.
		ALGR_TEKST	AGEGROUP_TEXT	Textual description of the age groups. E.g. "Sows/piglets", "weaners", "slaughter pigs".
		DWALGR_TEKST	DWAGEGROUP_TEXT	Alphanumeric field with the age groups' textual description and number codes merged together.
		STANDARDDYR_VAEGT	STANDARDANIMAL_WEIGHT	Standard weight for a given age group.
Instrumental variables	Present in most or all datasets	ID	ID	Unique identifier or a record (row) in a dataset. Serves as linking variable in other datasets. E.g. ID numbers from VTS_PRODUCT appear in other sets as PRODUCT_ID.
		DATO_OPRET	DATE_OPENING	Date in which a record was entered in the dataset.
		DATO_RET	DATE_CORRECTION	Last date a correction was made to a row.
		BRUGER_OPRET	USER_OPENING	Initials of the user who entered the row in the dataset.
		BRUGER_RET	USER_CORRECTION	Initials of the user who last made a correction to the row.

Dataset		Variables		
Name	English name and description	Name	Name in English	Description(a)
VTS_VARE	VTS_PRODUCT Product information at label level	VARE_NR	PRODUCT_NR	Identification number of the product. Not unique. Values can be re-used for new products when old ones are discontinued.
		VARE_TEKST	PRODUCT_TEXT	Name of the product described in that row.
		PAKNINGSTOER-RELSE	PACKAGESIZE	Number of sub-units in one package. E.g. one package may contain six flasks, or eight applicators, etc.
		ENHED_PAKNING	PACKAGE_UNIT	Unit of the sub-units contained in the package. E.g. bottle, applicator, envelope.
		MAENGDE	AMOUNT	Quantity of the preparation contained in each sub-unit. E.g. a bottle with 500 mL will have the value "500".
		ENHED_MAENGDE	AMOUNT_UNIT	Unit of the preparation contained in the sub-unit. E.g. mL, grams, etc.
		ATC_KODE	ATC_CODE	Anatomical Therapeutic Chemical (ATC) Classification System code for the active ingredients or combinations in the preparation (b).
		DATO_TIL	DATE_TIL	Date until which prescriptions of a registered product will be accepted in Vetstat. Normally filled with the default value "31122099".
		FODERMEDICIN	FOODMEDICINE	Dichotomous variable. If the product is supposed to be mixed in food, the value "1" is typed in, otherwise, "0".
		VDIS_ID	FORMULATION_ID	Linking variable with dataset VTS_FORMULATION.
		STYRKENOTAT	CONCENTRATION-MEMO	Total solid concentration of active ingredient found in the product, with units for the numerator and denominator. E.g. "150 mg/ml" or "100 IU/ml".
		IE_OMREGN	IU_CONVERSION	Numerical value of the preparation quantity in International Units (IU).
		ML_OMREGN	ML_CONVERSION	Numerical value of the preparation quantity in mL.
		DS_OMREGN	DS_CONVERSION	Numerical value of the preparation quantity in doses.
		REFP_ID	ASK ERIK	Assigns when the pharmacy hands out another, but similar product to the one prescribed. Mostly used by the cattle database (Kvægdatabasen).

Dataset		Variables		
Name	English name and description	Name	Name in English	Description(a)
VTS_VARE_AKTIVT_STOF	VTS_PRODUCT_ACTIVE_INGREDIENT Active ingredient and concentration information, as connected to each product	VARE_ID	PRODUCT_ID	Linking variable with dataset VTS_PRODUCT.
		AKTS_ID	ACTIVEINGREDIENT_ID	Active ingredients present in the preparation coded as numbers. Links with variable ID in dataset VTS_ACTIVE_INGREDIENT for textual values.
		STYRKE	CONCENTRATION	Numerical value of the total solid concentration of one active ingredient in the product.
		ENHED_STYRKE	CONCENTRATION_UNIT	Unit of the solid part of the concentration (numerator). E.g. gram, mg, mL.
		ENHED_PR_ENHED	UNIT_PER_UNIT	Unit of the concentration denominator, as related to the product administration form. E.g., mL (solutions), mg (powders), tablet, applicator, etc.
		IE	IU	Numerical value of the solid part of the ingredient in IU. Variable not used. Instead, see variable IE in dataset VTS_ACTIVE_INGREDIENT.
		IE_PR_ENHED	IU_PER_UNIT	Unit of the concentration denominator. Variable not used. Instead, see variable PER_UNIT in dataset VTS_ACTIVE_INGREDIENT.
VTS_AKTIVT_STOF	VTS_ACTIVE_INGREDIENT Active ingredient information, as related to international units and antibiotic groups	AKTIVT_STOF	ACTIVE_INGREDIENT	Textual active ingredient name.
		IE	IU	Numerical value for the numerator of the active ingredient concentration in IU.
		PR_ENHED	PER_UNIT	Unit of the concentration denominator in IU, as related to the product administration form. E.g., mL (solutions), mg (powders), tablet, applicator, etc.
		VSANTIBIO_ID	VSANTIMICRO_ID	Antimicrobial group, coded as numerical values. Linking variable with dataset VTS_ANTIMICROBIALGROUP.

VTS_ANTIBIOTIKAGRUPPE	VTS_ANTIMICROBIALGROUP Antimicrobial groups, textual values	ANTIBIOTIKAGRUPPE	ANITMICROBIALGROUP	Textual names of antimicrobial groups to which the active ingredients belong.
VTS_DISPENSERING	VTS_FORMULATION Administration routes and therapeutic forms	DISPENSERINGSFORM	FORMULATION	Product formulation. E.g. tablet, applicator, nose spray.
		VDISPGRP_ID	VDISPGRP_ID	Linking variable with dataset VTS_FORMULATIONGROUP. Administration route groups (oral, parenteral, others), coded as numerical values.
VTS_DISPGRUPPE	VTS_FORMULATIONGROUP Administration routes and therapeutic forms, grouped	DISPGRUPPE	ADMINISTRATIONROUTE	Textual names of administration route groups. E.g. "oral", "parenteral".

VTS_DYREKVALENT	VTS_ANIMALDOSE	VARE_ID	PRODUCT_ID	Linking variable with dataset VTS_PRODUCT.
		DYREART	ANIMALSPECIES	Number code of the species of the animal for which the product was prescribed.
		DOSIS_MAENGDE	DOSIS_AMOUNT	Numerical value for the amount of product preparation corresponding to one treatment dose per kg live weight..
		ENHED_DOSIS	DOSIS_UNIT	Unit for the amount of product (numerator) in the dose.
		PR_ENHED	PER_UNIT	Unit of the animal live weight (denominator) in the dose, normally in kg. Pre-dosed products have the unit "ds." or "tablet" in the numerator and denominator.
Instrumental variables	Present in most or all datasets	ID	ID	Unique identifier or a record (row) in a dataset. Serves as linking variable in other datasets named as an abbreviation of the dataset of origin followed by "_ID". As an example, ID numbers from VTS_PRODUCT appear in other sets as PRODUCT_ID.
		DATO_OPRET	DATE_OPENING	Date in which a record was entered in the dataset.
		DATO_RET	DATE_CORRECTION	Last date a correction was made to a row.
		BRUGER_OPRET	USER_OPENING	Initials of the user who entered the row in the dataset.
		BRUGER_RET	USER_CORRECTION	Initials of the user who last made a correction to the row.

- a) Descriptions and code interpretation based on the legislation for reporting of information for drug statistics, by the Danish Ministry of Health (original title "*Bekendtgørelse om indberetning af oplysninger til lægemiddelstatistik*", Sundheds- og Ældreministeriet). Available from <https://www.retsinformation.dk/pdfPrint.aspx?id=135928>.
- b) World Health Organization Collaborating Centre for Drug Statistics Methodology. WHOCC ATC/DDD Index 2015. Available from http://www.whocc.no/atc_ddd_index/

5.2 Paper II

Reporting the national Danish pig antimicrobial consumption: Influence of assigned daily dosage values and population measurement.

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Reporting the national Danish pig antimicrobial consumption: Influence of assigned daily dosage values and population measurement.

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Abstract

Background Transparent calculation methods are crucial when investigating trends in antimicrobial consumption over time and between populations. Until 2011, one single standardized method was applied when quantifying the Danish pig antimicrobial consumption with the unit “Animal Daily Dose” (ADD). However, two new methods for assigning values for ADDs have recently emerged, one implemented by DANMAP, responsible for publishing annual reports on antimicrobial consumption, and one by the Danish Veterinary and Food administration (DVFA), responsible for the Yellow Card initiative. In addition to new ADD assignment methods, Denmark has also experienced a shift in the production pattern, towards a larger export of live pigs. The aims of this paper were to 1) describe previous and current ADD assignment methods used by the major Danish institutions and 2) to illustrate how ADD assignment method and choice of population and population measurement affect the calculated national antimicrobial consumption in pigs (2007 to 2013).

Results The old VetStat ADD-values were based on SPCs in contrast to the new ADD-values, which were based on active compound, concentration and administration route. The new ADD-values stated by both DANMAP and DVFA were only identical for 48% of antimicrobial products approved for use in pigs. From 2007 to 2013, the total number of ADDs per year increased by 9% when using the new DVFA ADD-values, but decreased by 2% and 7% when using the new DANMAP ADD-values or the old VetStat ADD-values, respectively. Through 2007 to 2013, the production of pigs increased from 26.1 million pigs per year with 18% exported live to 28.7 million with 34% exported live.

In the same time span, the annual pig antimicrobial consumption increased by 22.2%, when calculated using the new DVFA ADD-values and pigs slaughtered per year as population measurement (13.0 ADDs/pig/year to 15.9 ADDs/pig/year). However, when based on the old VetStat ADD values and pigs produced per year (including live export), a 10.9% decrease was seen (10.6 ADDs/pig/year to 9.4 ADDs/pig/year).

Conclusion: The findings of this paper clearly highlights that calculated national antimicrobial consumption is highly affected by chosen population measurement and the applied ADD-values.

Keywords

Animal Daily Dose, antibiotics, antimicrobials, pigs, surveillance

Background

In recent years there has been an increasing concern towards the occurrence of antimicrobial resistance in both human and veterinary pathogens. This has led to a rise in the monitoring of veterinary antimicrobial usage [1] enabling detailed reports on antimicrobial consumption levels [2-5]. To minimize misinterpretations due to calculation method, it is crucial that reports on antimicrobial consumption are easily understandable and transparent [6, 7], especially when evaluating consumption over time and when comparing different animal populations – e.g. different countries [2, 8, 9].

In Denmark, detailed data on veterinary antimicrobial consumption from the national database VetStat [10] are summarized and published in yearly DANMAP-reports and on the Danish Veterinary and Food Administration's (DVFA) webpage [11, 12]. Furthermore, DVFA draws up monthly reports on pig antimicrobial consumption at herd level in conjunction with the antimicrobial restrictive legislation, known as the Yellow Card initiative [13]. DANMAP and DVFA both report anti-

microbial consumption using the measurement unit “Animal Daily Dose” (ADD) [14, 15]. Previously, both DANMAP and DVFA used the same set of standardized values for weight at treatment and dosage per kg body weight (ADD-value) when calculating the consumption as number of ADDs. The ADD-values were assigned at product level in VetStat and based on the approved dosage in the Summary of Product Characteristics (SPC), but in principle adjusted so the same quantity of active compound, concentration and administration route resulted in the same ADD count [15]. In 2011, new products emerged with a considerably higher SPC approved dosage compared to identical competing products. Due to substantial differences in SPC approved dosages, the previous standardization in VetStat was not possible. These products' ADD-values in VetStat were then based solely on the dosage value stated in the SPC. Consequently, products with the highest SPC dosage value were favored on the market as they resulted in a lower ADD count at herd level compared to similar products. This created a need for non-SPC based ADD-values to eliminate bias when evaluating the true resistance selective pressure. A new set of ADD-

values was therefore introduced in the DANMAP 2012-report. The new DANMAP ADD-values were based solely on active compound, concentration and administration route [16]. Later in spring 2014, DVFA also introduced a new set of ADD-values, which was implemented on the 30th of November 2014 and applied in the Danish Yellow Card initiative [17].

To take the population at risk into account when reporting the antimicrobial consumption, DANMAP uses both data on number of produced animals and data on number of live animals present [12, 18] and DVFA uses data from the Central Husbandry Register, which keeps records on number of pigs registered in each herd [19]. The chosen population measurement may affect the calculated antimicrobial consumption [20, 21]. This is especially true for Denmark, which has experienced a large shift in production pattern. In 2000, Denmark produced 22 million pigs of which 6% were exported live. Through 2007 to 2013, the production of pigs increased from 26.1 million pigs per year with 18% exported live to 28.7 million with 34% exported live [22, 23]. Of the exported pigs in 2013, 91.9% weighed approximately 30 kg at export [23]. In 2012, 7-30 kg pigs were reported to consume 77% of the total Danish pig antimicrobial consumption calculated in number of ADDs [24]. Excluding the exported live pigs when summing up antimicrobial consumption per produced pig might therefore lead to skewed results.

Several papers have investigated the consequences of using different measurement units when reporting antimicrobial consumption [3, 7, 25]. Additionally, a paper

was recently published on how the calculated Dutch pig antimicrobial consumption in 2012 was affected by using three different sets of ADD-values [26]. However, to our knowledge no paper has yet been published which both describes how choice of population measurement and set of ADD-values affect findings when evaluating the national veterinary antimicrobial consumption over time.

The aims of this paper were therefore 1) to describe the previous and present methods used by two major Danish institutions to assign ADD-values and 2) to illustrate how differences in choice of population and assigned ADD-values affect the calculated national pig antimicrobial consumption in the years surrounding the introduction of the Yellow Card initiative (2007-2013).

Methods

The study was performed as a retrospective database study.

Description of previous and present ADD-values

The three sets of ADD-values were collected from the relevant sources. The old VetStat ADD-values were extracted directly from VetStat on the 31st of March 2014. The new DANMAP ADD-values, applied in the DANMAP 2012 report, were collected from The National Food Institute, Technical University of Denmark (DTU) and the new DVFA ADD-values were downloaded from DVFA's webpage (<https://vetstat.dk>) on the 30th of December 2014. Only ADD-values for pigs were investigated. The three sets of ADD-value were compared and subjected to descriptive analyses to identify differences and similarities. Both ADD-values according to

DANMAP and DVFA may change over time as new products are added and other changes are made. The presented results on this paper therefore solely represent a snapshot in time.

Presenting antimicrobial consumption based on four different population measures and three different sets of ADD-values

Pig population measurements

To investigate how the chosen population affected the calculated national antimicrobial consumption, the Danish pig population was estimated according to the four following population measurements:

- 1) Number of pigs according to Statistics Denmark (SD). SD estimates the pig population in four quarterly surveys based on questionnaires from a random sample of 2500 pig herds [27]. The numbers are available to the public on SD's webpage. SD numbers are thought to represent live pigs present in the Danish herds at that particular point in time.
- 2) Number of pigs according to The Central Husbandry Register (CHR). This national database holds registrations on “*number of animals per age group present in the herd under normal circumstances*” [28]. Larger pig herds (>300 sows, ≥3000 finishers and/or 6000≥growers) are required to approve or update data on number of animals per herd minimum twice per year, while all other herds are required to approve or

update data to CHR a minimum once a year [29]. Data from CHR are used by DVFA in the Yellow Card initiative.

- 3) Number of pigs slaughtered in Denmark per year (SL-year). This number is published annually by the Danish Agriculture and Food Council [30].
- 4) Number of pigs produced per year (PROD-year). This number includes number of pigs slaughtered per year in Denmark and the number of live exported finishers, breeding gilts, sows and growers (exported at approximately 30 kg) and is published annually by the Danish Agriculture and Food Council [22, 23].

Calculation of antimicrobial consumption

Data on pig antimicrobial consumption from the 1st of January 2007 to the 31st of December 2013 were collected from the national database VetStat. The VetStat data

$$ADD = \frac{\text{Amount of product sold}^a}{\text{dosage pr kg body weight}^b * \text{standard weight}^c}$$

extraction was made the 31st of March 2014. VetStat contains detailed data on all veterinary drugs sold. A data entry in VetStat pertaining to a purchase of an antimicrobial product for use in production animals always contains: date of purchase, product purchased, amount of product, herd identification code and which age group and disease group the product has been prescribed for [10]. Data entries on pig antimicrobial consumption submitted by both pharmacies, veterinarians and feed

mills were included for the whole period (a total of 1,887,732 entries). Data entries from VetStat on antimicrobial purchase with a missing or invalid age group were excluded from the study (0.36%: 6,770 entries).

The national annual pig antimicrobial consumption was calculated in number of ADDs. To calculate number of ADDs the following must be known: quantity of product, dosage of product per kg body weight and the weight of the animal at treatment. Expected weight at treatment was set using the same standardized VetStat-values as both DANMAP and DVFA apply: growers (15 kg), finishers (50 kg) and pre-weaning pigs, sows, boars and gilts (200 kg). For dosage of product per kg body weight, the three collected sets of ADD-values were each applied - from VetStat (old VetStat ADD-values), DTU (new DANMAP ADD-values) and DVFA (new DVFA ADD-values).

Number of ADDs were calculated by using the same formula as VetStat, DANMAP and DVFA:

a: Antimicrobials registered per year for use in pigs according to VetStat data.

b: ADD-value according to either VetStat, DANMAP or DVFA.

c: Standardized VetStat-values for weight at treatment: growers (15 kg), finishers (50 kg) and pre-weaning pigs, sows, boars and gilts (200 kg).

Knowing the number of ADDs sold in a year, it was then possible to estimate number of ADDs per pig per year in relation to the four measurements for pig population: SD, CHR, SL-year and PROD-year.

For SD, CHR and SL-year, the total amount of antimicrobials recorded for use in pigs in VetStat was used when calculating ADDs/pig/year. However, for PROD-year, we needed to adjust the total consumption according to VetStat with an estimate of the extra amount of antimicrobials that were expected to be used, had these growers remained in Denmark. Firstly, not all exported growers would have survived until slaughter. We used an expected mortality of 3.8% (average finisher mortality 2007-2013 [31]) and reduced the number of would-have-been finishers accordingly. Secondly, we calculated the average antimicrobial usage in the finishing period in Denmark by dividing both total kg active compound and total number of ADDs (used for pigs > 30 kg) with the number of pigs slaughtered per year in Denmark (i.e. calculating average usage per finisher/year). Thirdly, we multiplied the adjusted number of exported growers (minus the 3.8%) with the average finisher antimicrobial usage and added this extra amount to the actual annual consumption as reported from VetStat.

Results and discussion

Description of the previous and present ADD-values

Both VetStat, DANMAP and DVFA have defined ADD as the assumed average maintenance dose per day for the main indication in a specified species [15, 18, 19]. The old VetStat ADD-values were based on the SPCs. In contrast, the new DANMAP ADD-values and the new DVFA ADD-values were solely based on active compound, concentration and administration route [19, 32]. Despite seem-

ingly identical theoretical foundations when determining a product's ADD-value, discrepancies between the new DANMAP ADD-values and the new DVFA ADD-values were observed.

VetStat listed ADD-values for 660 antimicrobial products for use in pigs, which included products intended for both oral, parenteral and intrauterine administration. DVFA listed ADD-values for 666 antimicrobial products for use in pigs, including products for parenteral, oral and intramammary use. DANMAP listed ADD-values for 636 antimicrobial products for pigs, including products approved for oral or parenteral use. DANMAP did not list ADD-values for intramammary or intrauterine antimicrobial products.

ADD-values stated by both DVFA and DANMAP were only identical for 48% (309/648) of the antimicrobial products approved for use in pigs. The mean percentage difference for the 339 products

with unequal ADD-values was 21.8% (std. dev.: 21.1; median: 20). This discrepancy between ADD-values, despite a seemingly identical theoretical foundation, may be due to the fact that DVFA has used "dosage for the most frequently used indication" as a starting point when deciding ADD-values [19], whereas DANMAP has used the dosage closest to the ones recommended in "The Veterinary Formula" published by the British Veterinary Association in 2005 [32].

Compared to the old VetStat ADD-values, 30.5% of the products had been assigned a new ADD-value by DVFA (203/666). The mean percentage difference for the 203 products with unequal ADD-value was 32.8% (std. dev: 33.4; median: 25). A few examples of products with differing ADD-values are shown in table 1.

Table 1. Example of products with changed ADD-value.

Product name	Active compound	Concentration	Gram or mL product per kg live weight (ADD value)					
			Old VetStat	New DANMAP		New DVFA		
			Actual ADD	Actual ADD	Change from Old VetStat	Actual ADD	Change from Old VetStat	Change from DANMAP
Lincomix Vet	Lincomycin	110 mg/gram	0.044	0.0454	3%	0.11	150%	142%
Aivlosin	Tylvalosin	8.5 mg/gram	0.25	0.5	100	0.25	0%	100%
Aquacycline Vet.	Tetracycline	180 mg/mL	0.04	0.0416	4%	0.056	40%	35%
Denagard Vet	Tiamulin	125 mg/mL	0.14	0.069	-51%	0.072	-52%	4%
Ladoxyn	Doxycycline	500 mg/gram	0.04	0.025	-38%	0.02	-50%	-20%
Suprim Vet.	Sulfa-TMP	120 mg/mL	0.21	0.25	19%	0.2	-4,8	-20%

Changes in the Danish pig population

Through 2007 to 2013, PROD-year was approximately twice as high as SD and CHR (*figure 1*). This is as expected as the average time from birth till slaughter is approximately 5-6 months. In the same time span, the Danish pig production increased by 10.3% from 26.1 to 28.7 million pigs per year when measured as PROD-year (*figure 1*). The difference between SL-year and PROD-year was caused by a shift in production pattern. From exporting 18% of produced pigs live in 2007, 34% were exported in 2013. This increase in live pig export was solely driven by a 161% increase in the export of live growers (3.5 million in 2007 to 9.2 million in 2013), as the export of live finishers and sows in the same time span decreased by 61% and 66%, respectively (finishers exported: 2007 899,439; 2013 350,447; sows exported: 2007 203,827; 2013 72,245). Through all years, number of sow slaughtered remained between 43,000 and 51,000.

Presenting antimicrobial consumption based on four different pig population measurements

From 2007 to 2013, the antimicrobial consumption, measured as total number of ADDs per year, increased by 9% when using the new DVFA ADD-values (278 to 303 million ADDs). However, the total consumption decreased by 2% and 7% respectively when using the new DANMAP ADD-values (280 to 273 million ADDs) and the old VetStat ADD-values (266 to 247 million ADDs).

Figure 2 illustrates how the chosen population measurement affects the calculated national average antimicrobial consumption per pig. When calculating the antimicrobial consumption using SL-year and the new DFVA ADD-values, the consumption increased by 22% from 2007 to 2013, whereas during the same time span the consumption increased by 4.5% when using PROD-year as population measure-

Number of pigs (mio.)

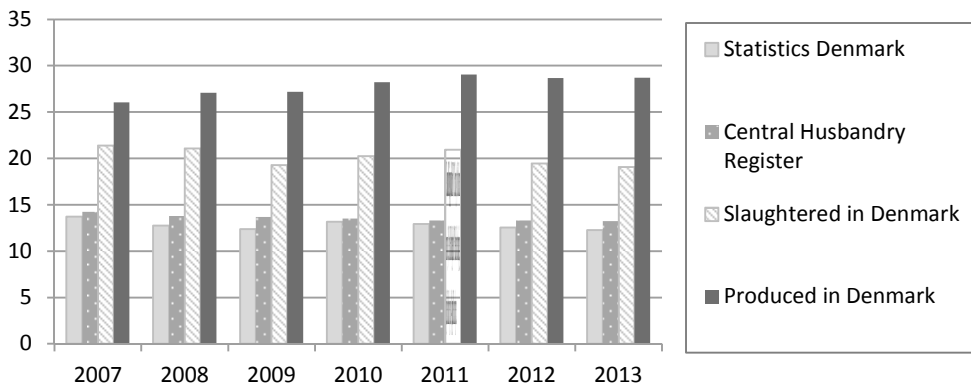


Figure 1. The annual Danish pig population. From 2007 to 2013 according to 1) Statistics Denmark's annual summer survey, 2) the Central Husbandry Register on the 31st of December in the corresponding year, 3) pigs slaughtered in Denmark per year and 4) pigs produced in Denmark per year.

ment. When the new DVFA ADD-values were applied, the national average antimicrobial consumption per pig was approximately twice as high when using SD or CHR as population measurements compared to PROD-year (e.g. in 2011: SD 20.0 ADDs/pig/year; CHR 19.5 ADDs/pig/year; PROD-year 9.6 ADDs/pig/year). In other words, the estimated number of standardized treatments per pig per year was twice as high when using number of pigs according to SD or CHR as when using It is not surprising that ADDs/pig/year based on PROD-year is comparably lower than when based on SD or CHR, as the number of pigs produced in a year will naturally be higher than the number of pigs

present at one single point in time. One could argue that i) SD or CHR and ii) SL-year or PROD-year should never be directly compared, as they represent fundamentally different ways of tallying up the pig population. However, the differences are illustrated in this paper to underline the necessity of clearly disclosing which population is used and illustrate how the choice can affect calculated results on antimicrobial consumption. In addition, it should here be underlined that ADD is strictly a theoretical unit, which is not necessarily reflective of the actual number of dosages used, as illustrated in previous studies [25, 33].

Antimicrobial consumption

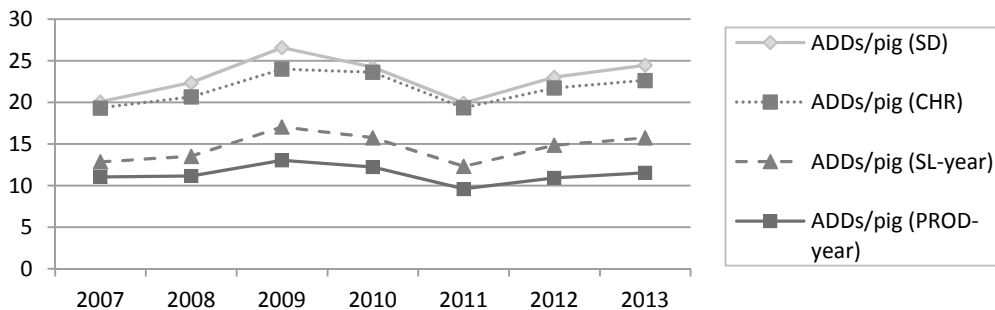


Figure 2. Annual antimicrobial consumption using four different measurements for the pig population. Number of Animal Daily Doses (ADDs)/pig/year calculated using the new DVFA ADD-values and the following four measurements for the pig population: 1) Statistics Denmark’s annual summer survey (SD), 2) number of pigs registered in the Central Husbandry Register on the 31st of December in the corresponding year (CHR), 3) pigs slaughtered in Denmark per year (SL-year) and 4) pigs produced in Denmark per year (PROD-year).

Based on these findings, it is evident that including or excluding live exported pigs highly affects the calculated results when estimating the national average antimicro-

bial consumption per pig. This especially holds true in a country such as Denmark, where a substantial part of the pigs are exported live after having reached 30 kg. Consequently, these pigs may have spent the period where they are most likely to

require the majority of their antimicrobial treatments in Denmark [24]. Not including the live export may lead to potentially faulty conclusions when estimating the national average pig antimicrobial exposure, as this calculation will be based on the assumption that all antimicrobials were consumed by the remaining pigs which were slaughtered nationally. Choice of population is also highly relevant when comparing antimicrobial consumption across borders. It is critical that researchers and other stakeholders take production demographics into account when reporting antimicrobial consumption, especially when comparing countries, such as Denmark or the Netherlands, with a large export of live growers, to countries with a large import of live pigs, such as Germany and Poland, or to countries which neither have a large import nor export, such as e.g. Sweden [34].

Presenting antimicrobial consumption based on three different sets of ADD-values

Figure 3 illustrates how the chosen set of ADD-values affects the calculated national average antimicrobial consumption per pig. If the consumption was calculated as gram active compound, number of ADDs using the old VetStat ADD-values or number of ADDs using the new DANMAP ADD-values with PROD-year as population measurement, a reduction was observed in the average antimicrobial consumption per pig from 2007 to 2013 (5.6%, 10.9% and 1.6% respectively). However, when using the new DVFA ADD-values, antimicrobial consumption per pig per year increased by 4.5% during the same time span. From 2011 and onwards, an increasing difference in the calculated consumption could be observed between the three different sets of ADD-values. When using PROD-year

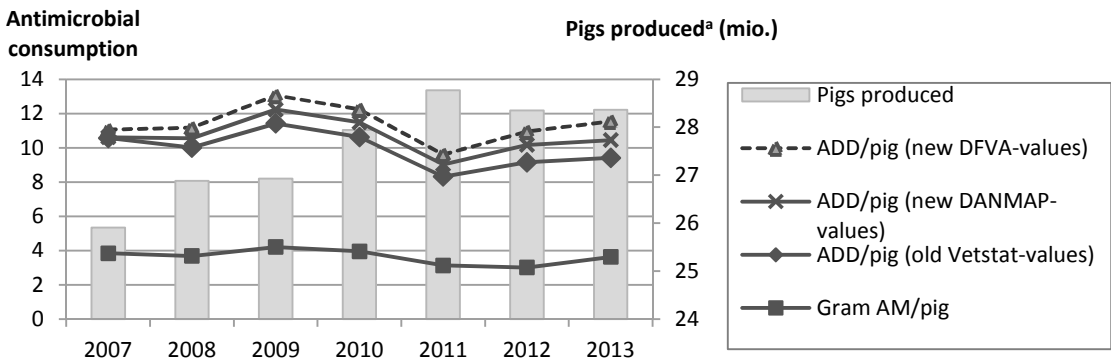


Figure 3. Annual antimicrobial consumption using three different sets of ADD-values. Number of Animal Daily Doses (ADDs)/pig/year calculated using PROD-year as population measurement and the following three sets of ADD-values: a) the old VetStat ADD-values used in the Yellow Card initiative until the 29th of November 2014, b) the DANMAP ADD-values used in the 2012 and 2013 DANMAP reports and c) the Danish Veterinary and Food Administration’s ADD-values used in the Yellow Card initiative from the 30th of December 2014 and onwards. aPigs produced adjusted for an assumed 3.8% mortality in exported growers.

as population measurement, the consumption was 15% higher in 2011 when using the new DVFA ADD-values (9.6 ADDs/pig/year) compared to the old VetStat ADD-values (8.3 ADDs/pig/year). In 2013, the calculated consumption was 23% higher when using the new DVFA ADD-values (11.6 ADDs/pig/year) than when using the old VetStat ADD-values (9.4 ADDs/pig/year).

This increasing difference may have been caused by a shift towards purchase of products which gave a low number of ADDs on paper and the release of several products with a higher approved dosage in the SPC compared to competing, similar products.

Presenting antimicrobial consumption based on four different pig population

measurements and three different sets of ADD-values

Twelve different ways of estimating the average annual antimicrobial consumption per pig arise when the four pig population measurements: 1) SD, 2) CHR, 3) SL-year and 4) PROD-year are combined with the three different sets of ADD-values: a) old VetStat ADD-values, b) new DANMAP ADD-values and c) new DVFA ADD-values). All twelve are shown in table 2 and graphically illustrated in figure 4.

In 2013, the calculated consumption amounted to 15.9 ADDs/pig/year when using SL-year and the new DVFA ADD-values, 13.0 ADDs/pig/year when using SL-year and the old VetStat ADD-values, 11.6 when using PROD-year and the new DVFA ADD-values and 9.4 when using PROD-year and the old VetStat ADD-values. So, compared to the calculated results when using SL-year and the new

Table 2. Annual antimicrobial consumption using four different population measurements and three different sets of ADD-values. Average annual antimicrobial consumption per pig calculated as number of ADDs/pig using four different pig population measurements: 1) number of pigs according to Statistics Denmark, 2) number of pigs according to the Central Husbandry Register, 3) pigs slaughtered in Denmark per year and 4) pigs produced in Denmark per year and using three different sets of ADD-values: a) the old VetStat ADD-values used in the Yellow Card initiative until the 29th of November 2014, b) the DANMAP ADD-values used in the 2012 and 2013 DANMAP reports and c) the Danish Veterinary and Food Administration's ADD-values used in the Yellow Card initiative from the 30th of December 2014 and onwards.

Population	Statistics Denmark			Central Husbandry Register			Slaughtered in Denmark			Produced in Denmark		
	Old VetStat	New DANMAP	New DVFA	Old VetStat	New DANMAP	New DVFA	Old VetStat	New DANMAP	New DVFA	Old VetStat	New DANMAP	New DVFA
2007	19,4	19,5	20,3	18,7	18,8	19,5	12,4	12,5	13	10,6	10,6	11,1
2008	20,3	21,4	22,6	18,7	19,7	20,9	12,3	12,9	13,7	10	10,5	11,2
2009	23,5	25,2	26,9	21,3	22,7	24,3	15,1	16,1	17,2	11,4	12,2	13,1
2010	21,2	22,9	24,4	20,7	22,3	23,8	13,8	14,9	15,9	10,6	11,5	12,2
2011	17,4	18,8	20	16,9	18,3	19,5	10,7	11,6	12,4	8,3	9	9,6
2012	19,2	21,3	23	18,2	20,1	21,7	12,4	13,8	14,8	9,2	10,2	10,9
2013	20,2	22,5	24,7	18,7	20,8	22,9	13	14,4	15,9	9,4	10,4	11,6

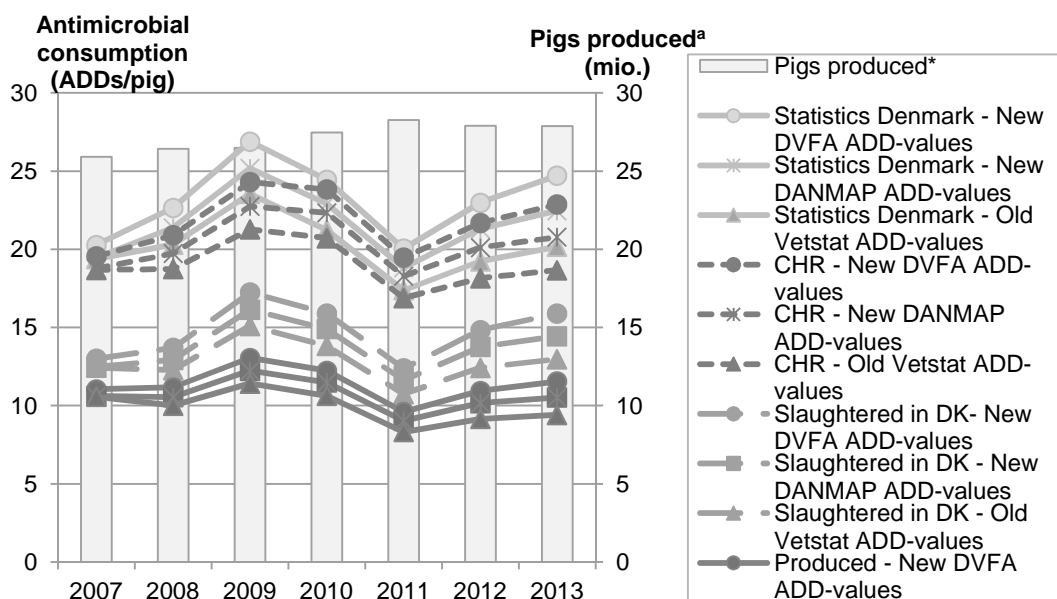


Figure 4. Annual antimicrobial consumption using four different population measurements and three different sets of ADD-values. Average annual antimicrobial consumption per pig calculated as number of Animal Daily Doses (ADDs)/pig using four different pig population measurements: 1) number of pigs according to Statistics Denmark, 2) number of pigs according to the Central Husbandry Register, 3) pigs slaughtered in Denmark per year and 4) pigs produced in Denmark per year and using three different sets of ADD-values: a) the old VetStat ADD-values used in the Yellow Card initiative until the 29th of November 2014, b) the DANMAP ADD-values used in the 2012 and 2013 DANMAP reports and c) the Danish Veterinary and Food Administration's ADD-values used in the Yellow Card initiative from the 30th of December 2014 and onwards. aPigs produced adjusted for an assumed 3.8% mortality in exported growers.

DVFA ADD-values, the consumption in 2013 was 40.8% lower when calculated based on PROD-year and the old VetStat ADD-values. This underlines how not including exported live pigs may highly alter the calculated results on antimicrobial usage, especially for a country such as Denmark with a substantial export of live pigs.

From 2007 to 2013, the antimicrobial consumption increased by 22% when using either SD or SL-year as population measurement and the new DVFA ADD-values. However, if PROD-year was used as population measurement together with the old

VetStat ADD-values, the consumption from 2007 to 2013 decreased by 10.9%.

Following the announcement of the Yellow Card initiative, the antimicrobial consumption, calculated as ADDs/pig, decreased by ~20% from 2010 to 2011 regardless of calculation method (table 2). The increase in antimicrobial consumption from 2011 to 2013 was in contrast influenced by chosen calculation method with 13.1% as the smallest increase observed (PROD-year/old VetStat ADD-values) and 28.3% as the largest increase (SL-year/new DVFA ADD-values).

In a recent study by Taverne et al. [26], the Dutch pig antimicrobial consumption in 2012 was calculated with three different sets of ADD-values. Taverne et al. reported that the calculated antimicrobial consumption was highly affected by the chosen set of ADD-values for a single point in time. This result is in concurrence with the findings of this study, which additionally found that not only are the results affected when evaluating the consumption as one point in time, but also when evaluating trends in consumption over time.

This study only investigated ADD-values described for one country. However, recently a call has been made by the European Surveillance of Veterinary Antimicrobial Consumption consortium for a standardized set of ADD-values to be applied in all European Union member states when reporting veterinary antimicrobial usage [35]. However, this may be no easy task. In addition to differing within countries, ADD-values have also been reported to differ between countries [26], e.g. due to i) differences in theoretical foundations, or ii) products having been assigned an ADD-value in one country and not in another [26]. Additionally, Postma et al. have reported differences in SPC stated dosages for products with identical active compound and administration route - both between and within countries [9]. This highlights the fact that even though two sets of ADD-values from different countries may have identical theoretical foundations, e.g. both being based on product SPCs, there is no guarantee that the two sets will be identical.

When a set of common ADD-values have been established, it is still vital that the

correct animal population is used as denominator, when attempting to assess true antimicrobial exposure. In a paper from 2013, Bondt et al. found that total sales data on all veterinary antimicrobials only gave a poor estimate of the actual antimicrobial exposure per animal species, as results were highly affected by the population demographics [8]. Bondt et al. recommended to use census data i.e. number of animals present at any given time (in this paper the equivalent to SD or CHR data), rather than number of animals produced when estimating the population at risk [8]. However, census data do not take turnover of animals into account. An estimation of the antimicrobial exposure in numbers of ADDs will often be reported as “numbers of ADDs/pig/year” or as “numbers of ADDs/pig/day”. A calculated result based on CHR as population measurement of e.g. 20 ADDs/pig/year will often translate into 20 treatments per pig per year. However, this is highly misleading. In Denmark, a grower on average spends seven weeks in the grower stable section, entering at 7 kg and leaving at 30 kg [36]. A herd with 500 growers registered in CHR will consequently have had roughly 3300 pigs through its facility in the course of one year, following the assumption that the herd stays empty for one week between each batch (53 weeks divided by 8=6.6; 6.6 multiplied by 500 registered pigs in CHR=3300 actual pigs). If it is then assumed that the previously mentioned 20 ADDs/pig/year is based on data from growers, the actual number of average treatments per pig will be 3.03 (20 divided by 6.6). The fact that estimations of antimicrobial exposure based on SD or CHR data do not take productivity into account might also potentially lead to herds with a

high production of pigs getting a higher consumption on paper when using CHR as a measurement for the population at risk. This even though the herd in fact may be using the same amount of antimicrobials per produced pig as a competing similar herd with a lower production. However, further studies are needed to discern the scope of this potential issue.

Conclusions

The findings of this study clearly highlight that calculated national antimicrobial consumption is highly affected by chosen population measurement and applied ADD-values. When SD or SL-year were used as population measurement together with the new DVFA ADD-values, a 22% increase was observed from 2007 to 2013 in the average antimicrobial consumption per pig, whereas the consumption in the same time span decreased with 11.3% when using PROD-year as population measurement together with the old VetStat ADD-values. These quite substantial differences may partly be due to the large shift in the Danish pig industry's production pattern with an increasing percentage of the produced pigs being exported to other countries before slaughter.

It is important to address the recent central change in ADD assignment regimen in Denmark, which occurred with the implementation of the two new sets of ADD-values by DANMAP and DVFA. Before 2012, the two main institutions to report the Danish pig antimicrobial consumption both utilized the exact same assignment method and the same set of ADD-values, which was located as a supplementary table in the VetStat database. However, as we

now have two major national institutions who calculate Danish pig antimicrobial consumption based on different sets of ADD-values, it becomes imperative to ensure that the exact calculation method is stated both for the numerator (antimicrobial consumption in e.g. total kg of active compound or number of ADDs) and the denominator (population measurement) when reporting antimicrobial consumption, especially to avoid comparisons of numbers across years based on different calculation methods. In conclusion, it is essential to ensure transparency in all calculations used when reporting antimicrobial consumption, especially when wishing to evaluate the consumption over time or compare with other countries.

Competing interests

None of the contributing authors have competing interests.

Authors' contribution

ND performed the data collection, the calculations and statistical analyses and drafted the manuscript. MF assisted in collecting data and helped to draft the manuscript. CSK aided in the design of the study, the statistical analyses and helped to draft the manuscript. NT aided in the design of the study and the statistical analyses. HS conceived the study and its design.

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5.3 Paper III

Changes in productivity and health in Danish weaners and finishers following introduction of the “*yellow card*” antimicrobial legislation.

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Changes in productivity and health in Danish weaners and finishers following introduction of the “yellow card” antimicrobial legislation.

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Abstract

In 2010, Denmark introduced legislation to lower the veterinary antimicrobial usage by penalizing pig herds with a high antimicrobial consumption. Following introduction of the legislation, popularly known as “the yellow card initiative”, national antimicrobial consumption decreased rapidly. The aims of this study were to investigate 1) how the reduction had been achieved according to veterinarians and herd managers and 2) if productivity and health in weaners and finishers had been affected by the sudden decrease.

The study was conducted in herds with ≥ 500 pigs at stable, which had decreased their annual antimicrobial consumption with $\geq 10\%$ following introduction of the yellow card initiative.

Questionnaire responses were submitted by 202 pig herds (response rate: 83%) and 58 veterinarians. Increased use of vaccines, less herd medication and staff education were the most frequent factors stated to have contributed to reducing antimicrobial usage.

Data on mortality and daily weight gain (DWG) were obtained from 49 weaner herds and 38 finisher herds. Data on lean meat percent (LMP) and lesions at slaughter were collected from 75 herds (841.948 pigs). A significant increase in weaner mortality was observed from 2.4% to 3.1% ($p=0.0001$). A trend towards lower weaner DWG was seen (447 to 436 grams/day). No

significant changes in finisher mortality, DWG or standard deviation of LMP at slaughter were observed. However, pig LMP increased significantly from 60.05 to 60.18 ($p < 0.0001$). Prevalence of 13 types of lesions at slaughter were investigated before and after introduction of the yellow card initiative, using a multilevel model (pig, batch and herd) with a binomial outcome. Significant increases in localized tail bites (OR= 1.8), chronic peritonitis (OR= 1.3) and abscesses in heads and ears (OR= 1.2) were observed ($p < 0.0001$). Chronic pleuritis (OR= 0.9), abscesses in front- mid- and rear section (OR= 0.84), chronic pneumonia (OR= 0.8), abscesses in feet and legs (OR= 0.7) and infected tail bites (OR= 0.4) all decreased significantly ($p < 0.0001$). Prevalence of osteomyelitis, chronic enteritis and chronic infectious arthritis did not change significantly. Chronic pleuritis had the highest herd median odds ratio (MOR) (19.9) and infected tail bites the highest batch MOR (2.03).

These findings suggest that lowering antimicrobial consumption through punitive legislation might not be without productivity consequences on a short term basis. It may therefore be prudent to consider relevant biological context when designing antimicrobial restrictive legislation. In line with this, the Danish government has recently announced a potential differentiated yellow card legislation.

Keywords

Pig, antimicrobial use, legal intervention, mortality, daily weight gain, lesions at slaughter

Abbreviations

DWG: Daily weight gain

LMP: Lean meat percent

ADD: Animal Daily Dose

MOR: Median odds ratio

1 Introduction

The increased number of antimicrobial resistant pathogens has led to a rising concern about imprudent use of veterinary antimicrobials. Since the late 1990s Denmark has marked itself as a frontrunner implementing several initiatives to reduce veterinary antimicrobial consumption (Aarestrup et al., 2010). At present, Denmark is one of the largest pig producers in the European Union (European Medicines Agency, 2012) with a substantial pig production compared to the relatively small human population. As an example, Denmark produced 27.6 million pigs in 2009 compared to a human population of 5.5 million people (Danish Agriculture and Food Council, 2009; Østberg, 2015). In 2009, the pig production accounted for 80% of the total veterinary antimicrobial consumption measured in kg of active ingredients (DANMAP, 2009). Consequently, specific emphasis has been placed on reducing antimicrobial usage in the pig production through initiatives, such as the cessation of antimicrobial growth promoters (Vigre et al., 2008) and the voluntary ban on cephalosporins (Agersø and Aarestrup, 2012).

One of the most recent legislative initiatives is known as the “yellow card initiative” (Jensen et al., 2014). The initiative was instigated in December 2010 following a widespread public debate prompted by an increase in the national pig antimicrobial consumption (Anonymous, 2015b). The yellow card initiative targets pig herds with a high antimicrobial consumption, based on an estimation of percentage pigs treated per day (Anonymous, 2014), and subjects them to fines and various punitive regula-

tions. Prior to instigation, a massive governmental effort was made to communicate the yellow card initiative directly to farmers, their organizations and the public in general. Furthermore, notification letters were dispatched to herds, whose antimicrobial consumption put them in the top twenty percentile. Consequently, a sharp decrease in the national antimicrobial consumption was detected as early as July 2010 (Andreasen et al., 2012).

At the time of notification letter dispatch only 5-10% of the Danish pig herds were above the Yellow Card threshold value (Anonymous, 2015b). However, the announcement led to a rapid 22% decrease in the overall national consumption from 104 tons active antimicrobial ingredients in 2009 to 81 tons in 2011 (DANMAP, 2009, 2011). There was consequently reason to believe that it was not only high consumer herds, who had lowered their antimicrobial consumption. In addition to the overall decrease in antimicrobial usage, the Danish annual pig production increased with 7% from 27.6 to 29.5 million pigs in the same time span (Danish Agriculture and Food Council, 2011). In comparison to other countries with similar intensive pig productions, the Danish pig industry’s antimicrobial consumption was already low prior to instigation of the yellow card initiative (European Medicines Agency, 2011), at 54.6 mg active ingredients/kg pork produced (DANMAP, 2009).

Implementation of the yellow card initiative was made possible through already existing national databases: VetStat containing detailed data on herd medicine purchase (Stege et al., 2003) and the Central Husbandry Register (CHR) containing information on population type and num-

ber of animals in each herd (Anonymous, 2013). As more and more countries are beginning to introduce databases similar to VetStat, the authors of this paper deemed it relevant to investigate whether productivity and health had been affected by the introduction of the yellow card initiative. This, especially as concerns have frequently been voiced internationally regarding detrimental effects of legislative bans on production and animal welfare (Casewell et al., 2003; Adjiri-Awere and Van Lunen, 2005; Liu et al., 2005; Hogberg et al., 2009).

In a paper from 2013, Alban et al. found changes in the prevalence of several types of lesions at slaughter before and after the introduction of the yellow card initiative (Alban et al., 2013). The study included all pigs sent to one large Danish abattoir and therefore gave an overall impression of the yellow card initiative's national impact on lesions at slaughter.

In this paper, it was specifically wished to investigate herds which had decreased their antimicrobial consumption following introduction of the yellow card initiative, regardless of previous level of antimicrobial usage. The aim was to investigate how the reduction in antimicrobial consumption had been accomplished and whether health and productivity had been affected. The hypotheses were that the drastic reduction in antimicrobials might have led to an increased number of lesions at slaughter, a change in mortality rate and a more uneven growth, indicated by an increased standard deviation in daily weight gain (DWG) and lean meat percent (LMP). Furthermore, it was hypothesized that herds with a high antimicrobial consumption prior to introduction of the yellow card initiative also

had a higher disease pressure and might therefore experience a larger change in mortality compared to herds with a lower antimicrobial consumption. The three specific objectives were therefore:

1. To investigate how the reduction in antimicrobial consumption following introduction of the yellow card initiative had been achieved according to veterinarians and herd managers
2. To investigate if the decrease in antimicrobial consumption following introduction of the yellow card initiative had caused a change in mortality rate and/or caused a more uneven growth rate, indicated by an increased standard deviation in DWG and LMP at slaughter
3. To investigate if the prevalence in lesions at slaughter had changed following the decrease in antimicrobial consumption.

2 Materials and methods

2.1 Study design

The study was performed as a retrospective, observational study in Danish pig production herds. The study period included the year before and the year after June 2010 - the month just prior to the dispatch of the first Yellow Card-notifications. Hence the study period in its entirety went from 1st of June 2009 to 31st of May 2011. In the following text "period 1" will refer to the year before introduction of the yel-

low card initiative (1st of June 2009-31st of May 2010) and “period 2” will refer to the year immediately following introduction of the yellow card initiative (1st of June 2010-31st of May 2011). Questionnaire, mortality and DWG data were double-typed manually into Excel 2013 Microsoft Office Package. Data management and analyses were carried out in SAS Enterprise 7.1.

2.2 Study population

Study herds were randomly selected among all Danish pig production herds which met the following inclusion criteria:

- 1) $\geq 10\%$ reduction in annual weaner or finisher antimicrobial consumption following the introduction of the yellow card initiative, measured in total kg of active ingredients (cut-off date: 1st of June 2010)
- 2) ≥ 500 pigs registered in CHR on the 31st of December 2010 in the same age group as the antimicrobial reduction was observed in.

In total, 2856 Danish pig production herds met the stated inclusion criteria. Of these, 650 study herds were selected by simple random sampling using the PROC SURVEYSELECT (SAS Enterprise 7.1).

2.2.1. Sample size justification

The sample size needed was calculated using PROC POWER (SAS Enterprise 7.1) for mean difference in a paired t-test. The calculation was based on findings on changes in weaner (7-30 kg) DWG following the cessation of use antimicrobial growth promoter use in 1999 (1998: 427 gram/day; 2000: 411 gram/day) (Kjeldsen and Callesen, 2006). With a standard devia-

tion of 50 gram/day, data from 79 herds were needed to document a change in DWG (power=0.8; $\alpha=0.05$), if it was assumed that the change following introduction of the Yellow Card legislation was similar to the changes seen in DWG after the cessation of antimicrobial growth promoter. In total, 650 study herds were contacted to correct for an expected exclusion rate of 55% and a non-participation rate of 30% with an expected inclusion and participation rate of 15%.

2.2.2. Respondent and exclusion rate

For each of the 650 herds, the main veterinarian was first contacted by phone and asked to introduce the project to the herd managers. This was done as pre-notifications have been found to increase response rates (Fox et al., 1988; Edwards et al., 2002). The main veterinarian was defined as the veterinarian who accounted for $\geq 50\%$ of the herd contact events in the study period. One contact event was defined as “a date on which prescription-only medicine had been sold to the herd”. If a herd’s main veterinarian only had contact events in either period 1 or period 2, the herd was categorized as having changed veterinarian during the study period and consequently excluded (22.5%; 146/650 herds). The herd was also excluded, if the veterinarian did not wish to introduce the study to the herd managers (3.4%; 22/650 herds; 3/105 contacted veterinarians). This was done to ensure uniformity in the data collection process. The remaining 482 herds (482/650 herds) were then contacted by phone for an initial phone interview.

The initial phone interview was conducted to discern whether a herd should be excluded and to ascertain availability of data

on mortality, DWG and/or LMP and lesions at slaughter. Phone interviews were performed by educated personnel (main author and two veterinary Master students). The phone interviews were conducted by reading aloud from a 2-page close-ended questionnaire to ensure identical wording of questions. The interviewed person was either the herd owner or the primary herd manager, if the herd owner was not responsible for the day-to-day management. Hereafter, both herd owner and primary herd manager will be referred to collectively as herd manager. The questionnaire can be obtained on request from the first author.

On contact, 32 herds did not wish to participate in the initial phone interview, 257 herds were included and 193 herds were excluded from the study (Table 1). Herds were excluded if they: (i) were organic, free-range or strictly breeding facilities, (ii) had no IT-based data reports on mortality or DWG, (iii) had closed down or changed ownership at any time point from start of study period to the time of data collection 2012 to 2013, (iv) had performed any major management or production changes during the study period, such as eradication programs, new buildings or a change in number of pigs (>10% change in number of pigs at stable) or (v) had experienced major acute disease outbreaks during the study. For finisher herds, two additional exclusion criteria were set: (1) if the herd had changed slaughter facility during the study period or (2) did not send produced finishers to the largest slaughter house conglomerate in Denmark (Danish Crown).

Table 1. Distribution of the initial randomly selected 650 study herds according to respondent rate, inclusion and exclusion.

	N	%
Included herds	257	39.5
Herd owner/manager response to questionnaire	202	31.1
Herd manager wanted to participate but never responded to questionnaire	55	
Veterinarian response to herd questionnaire	140	
Complete data on mortality –weaners	49	
Complete data on daily weight gain –weaners	43	
Data on lesions and lean meat percent at slaughter	75	
Excluded herds	339	52.2
Herd factors	47	7.2
Organic or free-range	2	0.3
No data on mortality or daily weight gain	21	3.2
Produced finishers not sent to Danish Crown for slaughter	17	2.6
Breeding facility	7	1.1
Changes during study period (1st of June 2009-31st of May 2011)	292	44.9
New primary veterinarian	146	22.5
Eradication program performed	49	7.5
Major disease outbreak (no other exclusion criteria met)	2	0.31
New owner or herd closure	34	5.2
Herd closure	36	5.5
New buildings	5	0.8
Change in number of pigs	14	2.2
Change in slaughter facility (no other exclusion criteria met)	6	0.9
Unknown inclusion/exclusion status as no answer to the initial questionnaire	54	8.3
Herd veterinarian did not wish to participate	22	3.4
Herd owner did not wish to participate	32	4.9

2.3 Questionnaire on how the reduction in antimicrobial consumption had been achieved

Herds, who wished to participate and were not excluded following the first phone interview, were asked to fill out a 1-page open- and close-ended questionnaire asking

how, according to the herd manager's perception, the reduction in antimicrobial consumption had been achieved in their particular herd. The herd managers had the option of choosing one or more of the following closed options: (a) increased use of vaccines, (b) smaller dosages of product,

(c) less herd medication, (d) shorter treatments, (e) education of personnel and (f) change of antimicrobial product. A text field was also provided to facilitate remarks on additional factors not stated in the closed options. A similar questionnaire was sent to each herd's primary veterinarian, asking how the veterinarian thought the herd's reduction in antimicrobial consumption had been achieved. The herd managers and veterinarians could choose between three ways of answering the questionnaire: (i) online (through freeonlinesurveys.com), (ii) as a hard copy which was then sent by postal mail with a stamped and addressed return envelope or (iii) as a phone interview conducted in a manner identical to the initial phone interview, with the interviewer reading the questions aloud from the questionnaire. The questionnaire can be obtained by contacting the first author.

A pilot study was performed by the test-retest method in 6 herds (four herd managers) to test for questionnaire reliability. The tests were performed with three weeks interval. All questionnaires were in Danish (native language of herd managers). The pilot group took between 3-10 minutes to fill out the questionnaire on how the reduction in antimicrobial consumption had

been achieved.

Agreement between herd manager and veterinarian was measured for each herd according to the closed statements (e-f) on factors contributing to reduced antimicrobial consumption. A simple Kappa statistic was calculated with PROC FREQ (SAS Enterprise 7.1).

2.4 Calculation of antimicrobial consumption

Data on herd antimicrobial consumption were collected from the national database VetStat. For initial selection of study herds, a data extraction from VetStat was performed the 20th of March 2012. Both purchase data registered by the pharmacies, veterinarians and feed mills were used. Of the entries on antimicrobial purchase 99.99% were registered by the pharmacies.

For the identification of herds who had reduced their antimicrobial usage with 10% or more, annual herd antimicrobial consumption was calculated as kilograms of active ingredients in period 1 and period 2, respectively.

For further descriptive analyses of the

$$ADDs = \frac{\text{Amount of product sold}^a}{\text{dosage pr kg live weight}^b * \text{standard weight}^b}$$

Formula 1. Calculation of Animal Daily Doses (ADDs) based on VetStat data.

$$ADD/100 \text{ pigs/day} = \frac{\text{ADDs purchased in given time period}}{\text{number of pigs according to CHR} * \text{days in time period}} * 100$$

Formula 2. Calculation of Animal Daily Doses (ADDs) per 100 animals per day based on VetStat and CHR data.

included study herds, antimicrobial consumption was calculated as (i) gram active ingredients per pig registered in the herd according to CHR per day and as (ii) Animal Daily Doses per 100 animals per day. Animal Daily Dose (ADD) was defined as “the average maintenance dose per day for the main indication in a specified species” as described by Jensen et al. (Jensen et al., 2004) and as applied in the yellow card initiative legislation (Anonymous, 2014). To calculate number of ADDs per 100 pigs per day, the total number of ADDs purchased in the given period must first be calculated. Number of ADDs is based on quantity of product purchased, dosage of product per kg live weight and weight of the pig at treatment. When estimating antimicrobial consumption based on VetStat data, only the exact amount of product purchased is known. Standardized database values are used for both weight at treatment and dosage per kg live weight (Formula 1). The VetStat standard weight values are 15 kg (weaners), 50 kg (finishers and unbred gilts) and 200 kg (pre-weaning pigs, sows, boars and bred gilts). Presently, three datasets on standard dosage values exist in Denmark. This study applied the dosage dataset collected directly from the VetStat database on 20th of March 2012.

The number of pigs treated per day can then be estimated as $\text{ADDs}/100 \text{ pigs/day}$ based on number of pigs present in each herd (Formula 2).

Data on number of pigs were collected from CHR, where number of pigs are registered at herd level according to age group: (i) weaners 7-30 kg, (ii) finishers >30 kg kept for slaughter and (iii) breeding animals (sows, gilts and boars). The obtained extraction from CHR contained number of

pigs in each herd divided into age groups on the 31st of December 2010.

2.5 Mortality and DWG

2.5.1 Data collection on mortality and DWG

The IT-based production reports containing data on mortality and DWG were collected by email or picked up by a project employee. Herds were excluded from investigation of changes in mortality or DWG, if the corresponding data (on mortality or DWG, respectively) were missing for more than 2 months in the entire study period or if the herd had less than three production reports per year.

2.5.2. Analyses of mortality and DWG

Most IT-based production reports in Denmark are made using the software program Agrosoft®. Production parameters in Agrosoft are summarized in production reports for a set period of time e.g. monthly, quarterly or biannually. In the Agrosoft production reports, mortality (given in percentage) is calculated based on number of pigs entering the facility minus the number of pigs leaving the facility during the specific period each production report covers. In the same way, DWG is also based on data summarized over an extended period of time, calculated as the total weight gain in the given period in kg divided by number of feed days in the period. The herd managers can themselves assign the time span which each production report covers. In practice, this means that the time span for production reports can vary greatly between herds. Some herds might have monthly production reports, some for three month periods and others again might have more irregular reports with e.g. one every month during winter

time and then a shift to production reports with a two or three months span. To take these irregularities in production report intervals into account when investigating changes in average mortality and DWG, weighted averages were calculated for each herd for the year before and after 1st of June 2010. The weighted averages were used to account for the fact that one report might cover a four month interval, and therefore representative of all four months, whereas other reports from the same herd might be on monthly intervals, and consequently only representative for one month periods. An example could be a herd with three quarterly reports (with mortality 2.1, 2.2 and 2.5, respectively) and three monthly reports in period 1 (with mortality 2.0, 1.9 and 1.7, respectively). The herd's average mortality in period 1 would then be calculated as:

With the three quarters spanning 92, 92 and 91 days and the three months 31, 28 and 31 days, respectively. The weighted averages for each period (before and after the introduction of the yellow card initiative) were then compared using a pairwise t-test.

For weaners an initial investigation of cor-

$$\frac{(2.1 * 92) + (2.2 * 92) + (2.5 * 91) + (2.0 * 31) + (1.9 * 28) + (1.7 * 31)}{365}$$

relation between change in mortality rate and change in antimicrobial consumption (both absolute and as percentage) was performed with a simple linear regression using PROC REG (SAS Enterprise 7.1). Furthermore, a separate analysis was carried out to investigate whether the change in mortality was different in herds with a high antimicrobial consumption in period 1

(≥ 25 ADD/100 pigs/day) compared to herds who had a lower antimicrobial consumption in the same time period (< 25 ADD/100/day). The analysis was performed using a PROC MIXED procedure (SAS Enterprise 7.1).

When investigating DWG standard deviation, the standard deviation of all submitted values on daily weight gain was first calculated at herd-level for period 1 and period 2, respectively. DWG standard deviation could then be evaluated using a repeated measurements analysis of variance (PROC MIXED, SAS Enterprise 7.1) with the log-transformed DWG standard deviation as outcome. The model is shown in its entirety in Table 2. For analysis, DWG standard deviation was log-transformed to meet the normal distribution criterion.

The initial calculations of DWG standard deviations were performed on original data, not weighted averages.

2.6 LMP and lesions at slaughter

Pigs with a live weight at slaughter > 130 kg were excluded from the investigation of changes in LMP and prevalence of lesions at slaughter. The Danish average hanging weight for finishers at slaughter was 82.2 kg in 2010 (Larsen, 2016). National average live weight was then estimated using a formula from the Danish Pig Research Centre: live weight = $1.38 * \text{slaughtered weight}$ (Kjelden, 2013), setting the average finisher live weight at slaughter to 113.4 kg.

Data on LMP and lesions at slaughter were collected directly from the abattoirs. The abattoirs routinely register lesions found at slaughter during meat inspection into an electronic database. The lesions are regis-

tered according to a standardized code (Alban et al., 2013). More than one type of lesion can occur on a single pig.

2.6.1 Analyses of LMP and lesions at slaughter

For all generalized mixed models used to evaluate LMP and lesions at slaughter, independent variables were: (i) period (before and after the introduction of the yellow card initiative) and (ii) seasons, divided into spring (March-May), summer (June-August), autumn (September-November) and winter (December-February). For all models it was also tested if there was significant interaction between period and season. The interaction statement was excluded from the final model, if the interaction was not significant ($p > 0.05$). All initial models are shown in their entirety in Table 2.

Changes in LMP and LMP standard deviation were each evaluated with a generalized linear mixed model for continuous outcome (PROC MIXED, SAS Enterprise 7.1). LMP was investigated at pig level with herd and batch as random effects and pig LMP as outcome variable. LMP standard deviation was investigated at batch level with herd as random effect and batch LMP standard deviation as outcome variable. For analysis, LMP standard deviation was log-transformed to meet the normal distribution criterion.

Prevalence of thirteen types of lesions at slaughter were investigated: abscess in front-, mid- or rear section, abscess in feet or legs, abscess in head or ears, abscess in the brain, chronic pleuritis, chronic pneumonia, chronic enteritis, chronic peritonitis, chronic pericarditis, chronic infectious arthritis, osteomyelitis, localized tail bite and infected tail bite. The changes in prevalence of lesions at slaughter were first investigated with simple statistical analysis (χ^2 and odds ratio) comparing the year before introduction of the yellow card initiative to the year after. Separate multivariate analyses were then performed for lesion types with a prevalence $> 0.01\%$ in the total study population. In total, eleven multivariate analyses were conducted, one for abscesses in front-, mid- or rear section, abscesses in feet or legs, abscesses in head or ears, chronic pleuritis, chronic pneumonia, chronic enteritis, chronic peritonitis, chronic infectious arthritis, osteomyelitis, localized tail bites and infected tail bites. The multivariate analyses were performed as generalized linear mixed models for binomial outcome analyzed at pig level with herd and batch as random effects (PROC GLIMMIX, SAS Enterprise 7.1). Median odds ratio (MOR) was calculated for the levels “batch” and “herd”. One batch was defined as pigs slaughtered on the same date from the same herd. MOR has by Merlo et al. been defined as the median value of the odds ratio between the

Table 2. Initial full models used to evaluate change in: (i) standard deviation of daily weight gain, (ii) lean meat percent, (iii) lean meat percent standard deviation and (iv) prevalence of lesions at slaughter.

Dependent variable	Independent variables included in the initial full model	Independent variables (random effect)
Daily weight gain standard deviation	= Period	Herd
Lean meat percent	= Period + season + interaction between period and season	Herd, batch
Lean meat percent standard deviation	= Period + season + interaction between period and season	Herd
Lesion at slaughter (yes/no)	= Period + season + interaction between period and season	Herd, batch

area of highest risk and the area of lowest risk (Merlo et al., 2006). In this study, the MOR therefore describes the median value of the odds ratio between a herd or batch with the highest odds and a herd or batch with the lowest odds e.g. the increased odds an individual pig (in median) would have if moving from the herd with the lowest odds to the herd with the highest odds of having that particular type of lesion at slaughter.

2.7 Statistical significance

For analyses of mortality and DWG statistical significance was set at $p=0.05$. However for analyses of LMP and lesions at slaughter, statistical significance was set at $p=0.01$ and odds ratio (OR) <0.9 or >1.1 due to the larger amount of observations.

3 Results

3.1 Questionnaire

In total, 202 herds submitted questionnaires on how the reduction in antimicrobial consumption had been achieved. 55 herds wanted to participate, but never responded to the questionnaire. When including herds not contacted due to the herd veterinarian not wishing to participate, this makes the total non-responding rate 16.8% (109/650 herds; 55 non-respondents (included herds, not meeting any exclusion criteria); 32 herds not wishing to participate; 22 herds where the main veterinarian did not wish to participate). In total, 58 veterinarians responded to the questionnaire (58/73 contacted veterinarians), accounting for 140 herds. For 106 herds both veterinarian and herd manager responded to the questionnaire. For 34

herds only veterinarians responded and for 96 herds only herd managers responded.

The frequencies of factors contributing to the reduction in antimicrobial consumption according to herd managers and veterinarians are shown in Figure 1 and 2. The most frequently stated factors were increased use of vaccines (51.5% of herd managers: 104/202 herds; 35.0% of the veterinarians: 49/140 herds) and less use of herd medication (44.1% of the herd managers: 89/202 herds; 57.9% of the veterinarians: 81/140 herds) (Figure 1-2).

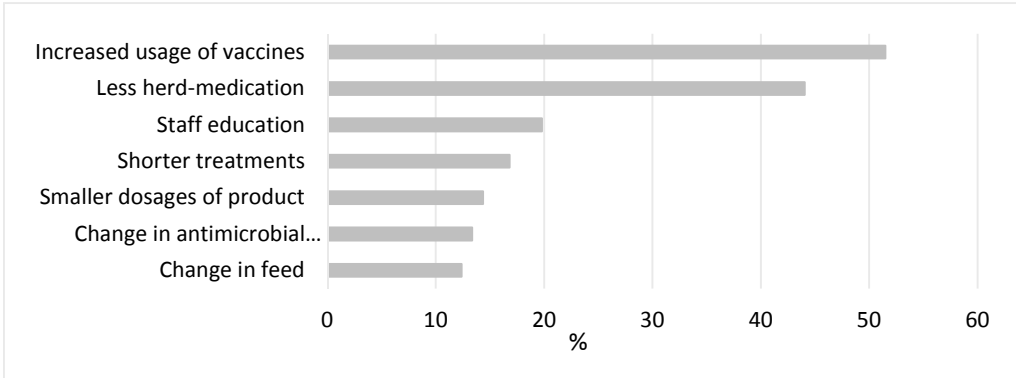


Figure 1. Factors contributing to the reduction in antimicrobial consumption as stated by the herd managers (202 herds).

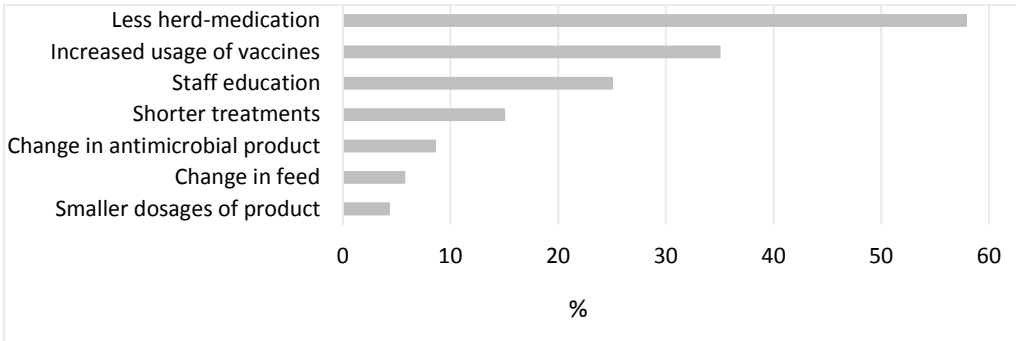


Figure 2. Factors contributing to the reduction in antimicrobial consumption as stated by the herds' primary veterinarians (58 veterinarians; 140 herds).

The most frequent factors, stated in the open text box were feed change (12.4% of the herd managers: 25/202 herds; 5.7% of the veterinarians: 8/104 herds) and better quality of purchased 7 and 30 kg pigs (6.4% of the herd managers: 13/202 herds; 12.1% of the veterinarians: 17/140 herds). Other marks from herd managers were improved cleaning procedures (11/202) and a higher accepted mortality rate (7/202), with statements such as:

“Tougher selection on which animals to cull”

“Earlier decision on whether to euthanize or not”

“Allows and accepts a higher mortality rate.”

Increased focus on all-in all-out production (5/202), increased focus on animal welfare (4/202), change in focus of veterinarian (2/202) and increased focus on climate control (2/202) were also mentioned. One herd manager, from a herd with an antimicrobial consumption close to the yellow card threshold prior to the introduction of the yellow card initiative, stated that he felt

unable to medicate based on knowledge and expressed fear of nurturing antimicrobial resistance due to faulty treatment regimens:

“We are more attentive.... In some cases we feel that we do not medicate based on veterinary knowledge, but solely out of a fear of receiving a yellow card penalty! This means a few more euthanized pigs, but perhaps also the risk of developing antimicrobial resistance due to suboptimal dosages”.

Of the veterinarians, 5.7% stated that the herds had used feed changes as a way to decrease their antimicrobial consumption (8/140). Furthermore an increased focus on animal welfare (7/140), established guidelines for initiation of treatment (5/140), establishing a section for 7-10 kg pigs (2/140) and an increased focus on daily care (6/140) were mentioned including statements such as:

“Better clinical observations”

“Better surveillance in the stable”

“Greater focus on day-to-day care of the pigs.”

One veterinarian stated that visual print-outs and monthly evaluations of the herd’s antimicrobial consumption had aided in reducing the antimicrobial consumption.

“Print-outs and follow-up on the antimicrobial consumption each month at the regular herd visit.

Graphs visible for all employees.”

In general herd managers and veterinarians had very poor agreement for all closed options, except for increased use of vaccines, where a fair agreement was observed (Table 3).

3.2 Weaners: Mortality and DWG

In total, 49 herds with weaners met all inclusion criteria for investigation of changes in mortality. Of these, 43 also had complete data on DWG. On average the weaner herds had approximately 3000 weaners registered in CHR (mean: 2934; min: 600; max: 11,000; standard deviation: 2071).

3.2.1 Description of weaner antimicrobial consumption

In the 49 participating herds with weaners, average weaner antimicrobial consumption in period 1 was 0.037 gram active ingredients per registered pig per day (standard deviation: 0.022). In period 2 the average antimicrobial consumption had decreased with 54% to 0.017 gram per pig per day (standard deviation: 0.009). This was equivalent to the 54% decrease found when calculating the consumption in ADDs per 100 pigs per day, which decreased from 20.2 (standard deviation: 12.9) to 9.3 ADDs per 100 pigs per day (standard deviation: 4.3). At the time of introduction of the yellow initiative, the set

Table 3. Agreement between herd manager and veterinarian regarding factors contributing to the herd’s reduced antimicrobial consumption sorted according to Kappa coefficient (106 herds).

	Prevalence		Kappa coefficient	95% confidence interval
	Herd manager	Veterinarian		
Vaccines	49.1% (52 herds)	32.1% (34 herds)	0.32	0.14-0.49
Smaller dosages of product	11.3% (12 herds)	4.7% (5 herds)	-0.07	-0.12; -0.02
Less herd medication	45.3% (48 herds)	57.6% (61 herds)	-0.02	-0.21; 0.16
Shorter treatments	13.2% (14 herds)	15.1% (16 herds)	-0.009	-0.19; 0.18
Staff education	21.7% (23 herds)	25.5% (27 herds)	0.007	-0.18; 0.20
Change in antimicrobial product	9.4% (10 herds)	14.2% (15 herds)	0.05	-0.16; 0.26

threshold value for weaners was 28 ADDs per 100 pigs per day. Of the included herds, 22% had an antimicrobial consumption of 25 or more ADDs per 100 pigs per day (11/49 herds), while 37% of the study herds had a consumption below 14 ADDs per 100 pigs per day, which was the approximate national average at the introduction of the yellow card initiative (Jensen et al., 2014).

3.2.2 Changes in weaner mortality

The average weaner mortality increased significantly with 27.1% from a 2.4% (standard deviation: 1.1) mortality to a 3.1% mortality (standard deviation: 1.5) ($p=0.0001$). No significant correlation between decrease in antimicrobial consumption and change in mortality was found when performing a simple linear regression analysis ($p=0.3$). However, herds with an antimicrobial consumption of ≥ 25 ADDs per 100 pigs per day in period 1 had a significantly higher increase in mortality compared to herds with a lower antimicrobial consumption ($p=0.02$). More specifically, herds with an antimicrobial consumption of 25 or more ADDs per 100 pigs per day in period 1 on average increased their mortality rate with 65% (standard deviation: 53.7), whereas herds with a lower antimicrobial consumption in period 1 on average increased their mortality with 25.6% (standard deviation: 47.7).

3.2.3 Changes in weaner DWG standard deviation

Together, both periods had a total of 258 observations from all herds. On average each herd had six observations per period (min: 3; max: 23). Overall the average DWG for all herds decreased from 447.0 (min: 255; max: 505) to 436.1 grams per

day (min: 271; max: 627). The average overall standard deviation increased from 43.2 in period 1 (min: 11.7; max: 199.7) to 48.1 in period 2 (min: 5.2; max: 114.2). No significant difference was found between the two periods for neither average DWG ($p=0.12$) nor standard deviation of DWG ($p=0.56$).

3.3 Finishers: Mortality and DWG

In total 38 finisher herds met all inclusion criteria for investigation of changes in mortality and DWG. On average the finisher herds had 1930 pigs registered in the herd (min: 530; max: 4100; standard deviation: 901.2). On average each herd had 5.8 observations per period (min: 3; max: 24).

3.3.1. Description of finisher antimicrobial consumption.

For the 38 finisher herds, the average antimicrobial consumption in period 1 was 0.035 gram active ingredients per registered pig per day (standard deviation: 0.026). In the following year, the average antimicrobial consumption decreased with 58.8% to 0.015 gram per pig per day (standard deviation: 0.009). This was almost equivalent to the 60.1% decrease found when calculating the consumption as ADDs per 100 pigs per day, which decreased from 6.13 (standard deviation: 4.2) to 2.4 ADDs per 100 pigs per day (standard deviation: 1.5). At the time of introduction of the yellow initiative, the set threshold value for finishers was 8 ADDs per 100 pigs per day. Of the included herds, only 24% had an antimicrobial consumption of 8 or more ADDs per 100 pigs per day (9/38 herds). Consequently, the remaining 29 herds decreased their antimicrobial consumption, even though they were not at risk of getting penalized by the yellow card initiative.

3.3.2 Changes in finisher mortality

The average mortality increased with 10.9% from a 3.3% (standard deviation: 1.3) mortality to a 3.7 % mortality (standard deviation: 2.3) in the year following the introduction of the yellow card initiative ($p=0.23$). No significant correlation was found between decrease in antimicrobial consumption and increase in mortality ($p=0.51$). When comparing high consumer herds to low consumer herds no discernible pattern could be distinguished with regards to changes in mortality rate.

3.3.3 Changes in finisher DWG standard deviation

The average DWG for all herds decreased from 890.2 (min: 669; max: 1015) to 886.6 grams per day (min: 654; max: 1006). The average overall standard deviation increased from 58.8 in period 1 (min: 6.6; max: 189.5) to 64.0 in period 2 (min: 17.0; max: 160.9). No significant difference was found between the two periods for neither average DWG ($p=0.71$) nor standard deviation of DWG ($p=0.43$).

3.4 Finishers: LMP and lesions at slaughter

75 herds with finishers met all inclusion criteria and had available data for the entire study period on LMP and lesions at slaughter. On average the herds had 1658 finishers in the herd at any given time (standard deviation: 845), with the smallest herd having 500 and the largest 5000 finishers according to CHR.

In total 841,948 finishers were sent for slaughter from the study herds in the study period (1st of June 2009-31st of May 2011), with 48.5% sent for slaughter in period 1 and 51.5% sent for slaughter in period 2.

On average the herds sent 11,226 pigs to slaughter during the entire study period (min: 2294; max: 27592; standard deviation: 5494). In total, 39.3 million finishers were slaughtered in Denmark during the entire study period (Danish Agriculture and Food Council, 2011). Number of finishers sent for slaughter in our study population constituted 2.1% of these.

For the 75 finisher herds included in the study on LMP and lesions at slaughter, the mean daily finisher antimicrobial consumption per pig in period 1 was 0.034 gram active antimicrobial ingredients. This decreased with 62% to 0.013 gram antimicrobials per pig per day in period 2. Measured as ADDs/100 pigs/day, the consumption on average decreased with 59.8% from 5.7 to 2.4.

3.4.1 Finishers: LMP at slaughter

The average LMP for all finishers sent to slaughter in period 1 was 60.05. LMP increased significantly to 60.18 in period 2 ($p<0.0001$). Significant effects of season and interaction between period and season were also observed ($p<0.001$).

The mean LMP standard deviation for all herds in period 1 was 4.4 (min: 268; max: 15.71; standard deviation: 1.729). This decreased to 4.2 in period 2 (min: 2.44; max: 11.78; standard deviation: 1.24). No statistically significant difference in LMP standard deviation was observed between period 1 and period 2 when taking batch into account ($p=0.64$). Furthermore, no significant effect of season was observed ($p=0.39$).

3.4.2.1 Lesions at slaughter – univariate analysis

Of the investigated lesions, chronic pleuritis was the most frequent lesion at slaughter found in 24.8% of all the finishers in the study population. Abscesses in the front- mid- and rear section, abscesses in the head and ears, and abscesses in the feet and legs were the second, third and fourth most prevalent at 1.8%, 1.5% and 1.4%, respectively. All other lesions had a <1% prevalence. No pigs were registered as having chronic pericarditis or abscesses in the brain at slaughter. Prevalence of all investigated lesions according to period are shown in Table 4 and according to both period and season in Figure 3-8. Pigs which had none of the investigated lesions at slaughter accounted for 69.63% (284,396/408,468 pigs) and 69.59% (301,679/433,480) in period 1 and 2, respectively.

When a simple univariate analysis (χ^2) was performed, a significant change in prevalence was found for all investigated lesions, except chronic pleuritis, chronic enteritis and chronic infectious arthritis (Table 4).

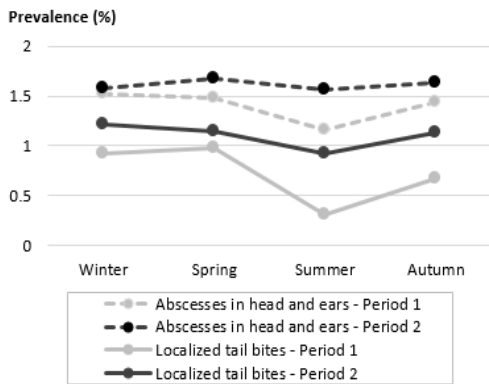


Figure 3. Prevalence (%) of localized tail bites and abscesses in head and ears according to period and season. Period 1: the year before introduction of the yellow card initiative (1st of June 2009-31st of May 2010). Period 2: the year after introduction of the yellow card initiative (1st of June 2010-31st of May 2011).

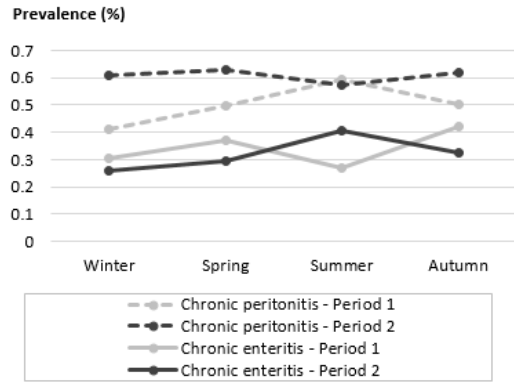


Figure 4. Prevalence (%) of chronic peritonitis and chronic enteritis according to period and season. Period 1: the year before introduction of the yellow card initiative (1st of June 2009-31st of May 2010). Period 2: the year after introduction of the yellow card initiative (1st of June 2010-31st of May 2011).

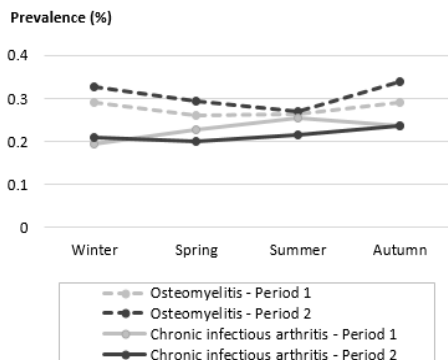


Figure 5. Prevalence (%) of osteomyelitis and chronic infectious arthritis according to period and season. Period 1: the year before introduction of the yellow card initiative (1st of June 2009-31st of May 2010). Period 2: the year after introduction of the yellow card initiative (1st of June 2010-31st of May 2011).

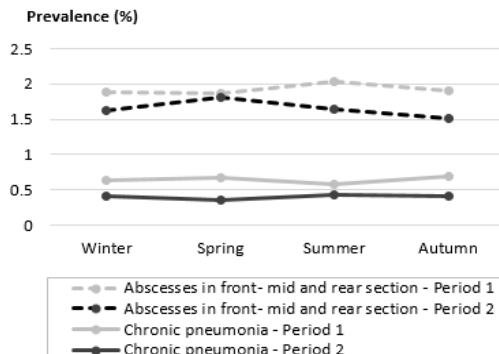


Figure 6. Prevalence (%) of chronic pneumonia and abscesses in front- mid- and rear section according to period and season. Period 1: the year before introduction of the yellow card initiative (1st of June 2009-31st of May 2010). Period 2: the year after introduction of the yellow card initiative (1st of June 2010-31st of May 2011).

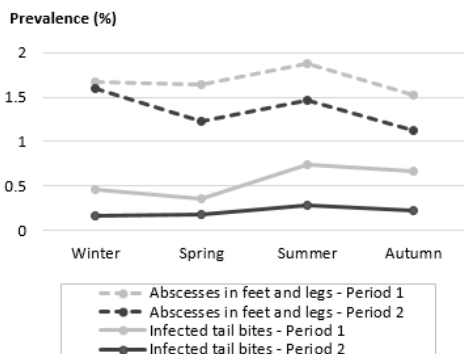


Figure 7. Prevalence (%) of infected tail bites and abscesses in feet and legs according to period and season. Period 1: the year before introduction of the yellow card initiative (1st of June 2009-31st of May 2010). Period 2: the year after introduction of the yellow card initiative (1st of June 2010-31st of May 2011).

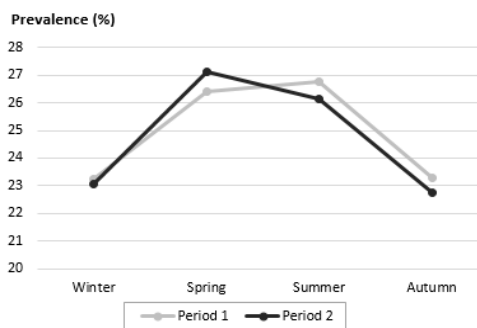


Figure 8. Prevalence (%) of chronic pleuritis according to period and season. Period 1: the year before introduction of the yellow card initiative (1st of June 2009-31st of May 2010). Period 2: the year after introduction of the yellow card initiative (1st of June 2010-31st of May 2011).

Table 4. Prevalence of lesions at slaughter in 841,949 Danish finishers sent for slaughter from 1st of June 2009 to 31st of May 2011. Sorted in descending order by odds ratio (OR) calculated using univariate analysis. Period 1: the year before introduction of the yellow card initiative (1st of June 2009-31st of May 2010). Period 2: the year after introduction of the yellow card initiative (1st of June 2010-31st of May 2011). Lesions at slaughter which changed significantly between periods are marked with *.

Lesion type	No. of pigs with lesions (%)		Period 1 compared to period 2	
	Period 1	Period 2	OR (95% CI)	P-value (chi-sq test)
Tail bites, localized*	2985 (0.73)	4777 (1.10)	1.51 (1.45-1.58)	<0.0001
Chronic peritonitis*	2030 (0.50)	2636 (0.61)	1.23 (1.16-1.30)	<0.0001
Abscesses in head and ears*	5752 (1.4%)	6989 (1.6%)	1.14 (1.11-1.19)	<0.0001
Osteomyelitis*	1132 (0.28%)	1239 (0.31%)	1.11 (1.02-1.20)	0.01
Chronic pleuritis	101575 (24.87)	107397 (24.78)	0.99 (0.99-1.01)	0.33
Chronic enteritis	1404 (0.34%)	1394 (0.32%)	0.94 (0.87-1.01)	0.08
Chronic infectious arthritis	931 (0.22)	934 (0.23)	0.95 (0.86-1.04)	0.22
Abscesses in front- mid- and rear section*	7836 (1.9%)	7157 (1.7%)	0.86 (0.83-0.89)	<0.0001
Abscesses in feet and legs*	6849 (1.68)	5345 (1.23)	0.73 (0.71-0.76)	<0.0001
Chronic pneumonia*	2630 (0.64%)	1758 (0.41%)	0.63 (0.59-0.67)	<0.0001
Tail bites, infected*	2260 (0.55)	920 (0.21)	0.38 (0.35-0.41)	<0.0001
Abscesses in the brain	0 (0)	0 (0)	na	na
Chronic pericarditis	0 (0)	0 (0)	na	na

3.4.2.2 Lesions at slaughter – multivariate analysis

The results of the multivariate model are shown in Table 5. A significantly higher prevalence in period 2 compared to period 1 was seen for localized tail bites (OR= 1.76), chronic peritonitis (OR= 1.29) and abscesses in head and ears (OR= 1.16) ($p < 0.0001$). No significant change between periods was observed for osteomyelitis (OR= 1.08), chronic enteritis (OR= 1.01) and chronic infectious arthritis (OR = 0.94). When analyzing the data using a simple univariate chi-square test prevalence of chronic pleuritis did not change significantly between periods ($p = 0.33$). However, when analyzing data with the multi-level model taking clustering of data into account, the change in prevalence between periods was found to be significant ($p < 0.0001$) with the odds of having chronic pleuritis 11% lower in period 2 compared to period 1 (OR= 0.89; 95% CI: 0.86-0.93). A significant decrease in prevalence in period 2 compared to period 1 was

also seen for abscesses in the front- mid- and rear section (OR= 0.84), chronic pneumonia (OR= 0.77), abscesses in feet and legs (OR: 0.74) and infected tail bites (OR: 0.40). That significance level for chronic pleuritis is affected by whether or not clustering is taken into account is compatible with the relatively high herd MOR for chronic pleuritis compared to the herd MOR for all other investigated lesions (herd MOR for chronic pleuritis: 19.88; 2nd highest herd MOR= 1.66 for infected tail bites). The highest batch MOR was observed for infected tail bites (MOR= 2.03) and the second highest for chronic enteritis (MOR= 1.87). Abscesses in front- mid- and rear section were found to have the lowest herd MOR (herd MOR= 1.0075) and chronic pneumonia to have the lowest batch MOR (MOR= 1.0050).

Model with lesion as dependent variable	Frequency of lesions in Period 2 compared to period 1															Complete model	
	Random effects				Fixed effects												
	Covariance subject	Parameter estimate	Standard error	MOR	Period		Season			Season fixed effect	Interaction ^a	Period					
					OR	P-value	Winter/Autumn	P-value	Spring/Autumn			P-value	Summer/autumn	P-value	OR	95% CI	
Tail bites, localized*	Herd	0.6920	0.122	1.579	1.76	<0.0001	1.20 (1.09-1.32)	0.37	1.17 (1.06-1.29)	0.65	0.57 (0.51-0.64)	0.0002	<0.0001	<0.0001	1.76	1.64-1.90	
	Batch	0.6296	0.032	1.456													
Chronic peritonitis*	Herd	0.3806	0.068	1.148	1.33	<0.0001	0.89 (0.80-1.00)	0.64	1.04 (0.93-1.16)	0.68	1.03 (0.92-1.15)	0.019	0.0365	0.0037	1.29	1.19-1.39	
	Batch	0.6212	0.0392	1.445													
Abscesses in head and ears*	Herd	0.2602	0.044	1.067	1.17	<0.0001	0.99 (0.93-1.05)	0.07	1.02 (0.96-1.09)	0.99	0.87 (0.82-0.93)	0.12	<0.0001	0.0005	1.16	1.11-1.21	
	Batch	0.1793	0.012	10.311													
Osteomyelitis	Herd	0.3017	0.059	1.091	1.08	0.09	0.95 (0.84-1.08)	0.44	0.87 (0.76-0.98)	0.03	0.85 (0.75-0.97)	0.015	0.04	0.39	1.08	0.99-1.18	
	Batch	0.4054	0.047	1.170													
Chronic enteritis	Herd	0.3522	0.072	1.126	0.84	0.82	0.78 (0.68-0.90)	0.05	0.94 (0.82-1.08)	0.55	0.91 (0.79-1.05)	0.02	0.006	0.0025	1.01	0.92-1.12	
	Batch	0.8112	0.056	1.873													
Chronic infectious arthritis	Herd	0.2261	0.050	1.050	1.01	0.196	0.84 (0.73-0.97)	0.21	0.91 (0.79-1.05)	0.12	0.99 (0.86-1.14)	0.31	0.06	0.22	0.94	0.84-1.04	
	Batch	0.4420	0.062	1.205													
Chronic pleuritis*	Herd	17.703	0.290	19.880	0.81	<0.0001	1.02 (0.97-1.08)	0.02	1.19 (1.13-1.26)	<0.0001	1.23 (1.16-1.30)	<0.0001	<0.0001	0.0006	0.89	0.86-0.93	
	Batch	0.5074	0.011	1.278													
Abscesses in front- mid- and rear section*	Herd	0.0884	0.016	1.008	1.19	<0.0001	1.03 (0.97-1.08)	0.12	1.08 (1.02-1.14)	0.0002	1.07 (1.02-1.14)	0.13	0.012	<0.0001	0.84	0.81-0.87	
	Batch	0.1120	0.001	1.012													
Chronic pneumonia*	Herd	0.5677	0.106	1.360	0.75	<0.0001	1.02 (0.87-1.19)	0.71	0.97 (0.83-1.14)	0.72	1.05 (0.90-1.23)	0.51	0.78	0.51	0.75	0.67-0.83	
	Batch	14.440	0.072	1.005													
Abscesses in feet and legs*	Herd	0.2168	0.038	10.459	0.74	<0.0001	1.04 (0.97-1.11)	0.83	1.07 (1.00-1.14)	0.097	1.23 (1.15-1.31)	<.0001	<0.0001	0.17	0.74	0.71-0.77	
	Batch	0.1857	0.013	1.033													
Tail bites, infected*	Herd	0.7280	0.136	1.658	0.36	<0.0001	0.67 (0.58-0.78)	0.0009	0.59 (0.51-0.69)	0.0113	1.09 (0.95-1.25)	0.50	<0.0001	0.0072	0.40	0.36-0.44	
	Batch	0.8621	0.058	2.032													

Table 5. Prevalence of lesions at slaughter in 841,949 Danish finishers sent for slaughter from 1st of June 2009 to 31st of May 2011. Sorted in descending order by period odds ratio (OR) for the complete generalized mixed model. Period 1: the year before introduction of the yellow card initiative (1st of June 2009-31st of May 2010). Period 2: the year after introduction of the yellow card initiative (1st of June 2010-31st of May 2011). Lesions at slaughter which changed significantly between periods are marked with *.

^a interaction between season and period.

4 Discussion

4.1 Study design

In this study, productivity and lesions at slaughter were compared for the year immediately before and the year immediately after the introduction of the yellow card initiative. However, it would have been optimal, if the two periods had been separated by a buffer period to avoid any spill-over effect from the first period into the second period. Unfortunately, this was not feasible. All included herds were to have had no major changes in management during the entire study period. Consequently, there was not enough manpower available on the project to contact the sufficient amount of herds needed in order to obtain an adequate amount of study herds.

The initial selection of herds with a decrease in antimicrobial consumption was done based on differences in total kg of active ingredient antimicrobials purchased in period 1 and period 2. Optimally, the consumption would initially have been calculated in ADDs/100 pigs/day, as this measurement takes both differences in population and product potency into account. However, the authors only had access to a single data extraction on number of pigs in each herd on the 31st of December 2010. As the measurement ADDs/100 pigs/day is highly sensitive to changes in animal numbers, it was decided not to use this measurement unit for initial selection of herds. Later on in the study, herds were subsequently excluded if they answered yes to having made any changes in herd size during the study period.

4.2 Bias and representativeness

As with any questionnaire risks exist that only herd managers participated, who had either an interest in research or the resourcefulness to take the time to answer, thereby potentially limiting the representativeness. This study had a non-response rate of 16.7% of all the initially selected herds, which reduces the inherent risk of non-representativeness.

This study is only representative of herds, which decreased their antimicrobial consumption with $\geq 10\%$ following the introduction of the yellow card initiative. Results from other populations may therefore differ from the findings presented in this paper.

4.3 Validity of data

Detailed data on all antimicrobials purchased from pharmacies or feed mills are automatically registered in VetStat (Jensen et al., 2004). For antimicrobials purchased through the veterinarian, the veterinarian is required by law to register the purchase data into VetStat (Anonymous, 2015a). There may still be a certain percent of antimicrobials sold by veterinarians, which are not registered in VetStat. However, for the pig antimicrobial consumption, 99.8% are purchased directly through the pharmacies (E. Jacobsen, personal communication).

Data on mortality and DWG were collected as IT-based productions reports. Both mortality and DWG are based on number of pigs entering the stable, number of pigs leaving the stable, weight at entry and weight at exit. As the study was performed retrospectively, using the already available data was therefore the most feasible solution.

Data on LMP and lesions at slaughter are registered by educated staff at the abattoirs (Alban et al., 2013). However, sensitivity and specificity for detection and classification of lesions at slaughter may differ between abattoirs (Enøe et al., 2003) and between individual staff members (Bonde et al., 2010). To minimize effect of abattoir, herds were excluded if they changed abattoir at any time point throughout the entire study period. Unfortunately, it was not possible to adjust for individual observer, as data on observer were not available. A conservative p-value ($p=0.01$) for analyses of lesions at slaughter was chosen in an attempt to minimize the risk of faulty conclusions and to take precautions for the large quantity of observations. However, conclusions on lesions with a low prevalence must still be interpreted cautiously, as these are more sensitive to inter- and intra-observer variation.

4.4 Factors contributing to a decreased antimicrobial consumption

At the introduction of the yellow card initiative, notification letters were only dispatched to herds with an antimicrobial consumption in the top twenty percentile. However, as seen in this study it was not only herds with a high initial antimicrobial consumption, who lowered their antimicrobial usage. Also herds with a relatively low antimicrobial consumption prior to the introduction of the yellow card initiative decreased their consumption. The large decrease in both high- and low-consumer herds may have been due to the threat of potential financial repercussions. This would correspond with previous studies, which have reported financial incentive as one of the herd managers' main drivers,

when choosing to implement new management or bio-security procedures (Gunn et al., 2008; Fraser et al., 2010; Valeeva et al., 2011; Laanen et al., 2014). Therefore, potentially making policy measures with financial incentives more effective than their non-financial counterparts (Visschers et al., 2015), inducing herd managers, who may have hesitated previously, to implement new procedures in an attempt to avoid potential penalties. Furthermore, increased mortality has also been stated as a major incentive to implement new disease control initiatives (Alarcon et al., 2014). However, some herd managers may decide that a higher mortality is acceptable in order to reduce their antimicrobial consumption sufficiently. In this study, seven herd managers explicitly stated that they accepted a higher mortality rate to keep their antimicrobial consumption at a lower level by culling diseased pigs earlier.

Increased use of vaccines was the method most frequently stated by herd managers (52%) to have contributed to the reduction in antimicrobial usage. This is not surprising, as vaccines have great value in combating diseases (Mateusen et al., 2001; Stevens et al., 2007) and new vaccination regimens can easily be tested (Postma et al., 2015). In general, most of the stated initiatives, such as staff education, feed changes and increased focus on cleaning procedures, could be implemented over a relatively short time span and without major financial investments. Studies have shown that improved management (Arnold et al., 2004; Laine et al., 2004) and external facilities (Wierup, 2001) are major factors in reducing antimicrobial consumption without productivity losses. However, financially costly initiatives, such as reinvestment in

buildings and farm infrastructure, may not be financially possible for many pig producers in the present economic climate (Alarcon et al., 2014; Speksnijder et al., 2015). Consequently, some herd managers might hesitate to lower the antimicrobial usage, if they feel antimicrobials are needed to keep production costs low (Coyne et al., 2014). A potential risk may be that herds with an already strained economy will not be able to implement new and potentially costly management procedures and will consequently either suffer the penalties or close.

Shorter treatments were stated by 17% and smaller dosages by 14% of herd managers, as having aided in reducing the antimicrobial usage. Further studies are needed to discern whether the treatment regimens currently applied are now in line with veterinary recommendations, as sub-therapeutic levels may increase the risk of developing antimicrobial resistance (Olofsson and Cars, 2007).

A very poor agreement between herd manager and veterinarian was observed for nearly all of the closed options on initiatives implemented to reduce antimicrobial consumption. For vaccines, however, agreement between herd managers and veterinarians was fair. This may be because vaccines must be prescribed by the veterinarian. The probability that the veterinarian and herd manager will both remember an increase in vaccines might therefore be relatively higher.

When reviewing the results of this study, it must be kept in mind that all herds in the initial selection process were excluded if any major changes, such as eradication

programs or new buildings, had been performed during the study period. These herds were therefore not shown in the Results chapter. However, from the initial phone interview on exclusion criteria, it is known that 7.5% of the initial 650 study herds performed an eradication program on at least one time point during the study period. According to a report published by the Danish industry organization Danish Agriculture and Food Council, no particular increase in eradication programs was seen in relation to the introduction of the yellow card initiative (Danish Agriculture and Food Council, 2015). Further research is needed to establish if the occurrence of eradication programs in the chosen study population is similar to that in other herds, which lowered their antimicrobial consumption in the same period.

4.5 Mortality and DWG

In herds which decreased their antimicrobial consumption $\geq 10\%$ weaner mortality increased significantly from 2.4% to 3.1% following the introduction of the yellow card initiative. Furthermore, trends were observed towards a lower average weaner DWG (447 to 436 grams per day) and a slightly larger DWG standard deviation (from 43.2 to 48.1). None of the trends were found to be significant. However, this may be caused by the relatively small study population (49 herds), which only accounted for 62% of the number of herds needed according to the initial sample size calculation. For finishers, a trend was observed towards a higher mortality (3.3% to 3.7%), lower average daily weight gain (890 to 867 grams per day) and higher average daily weight gain standard deviation (58.8 to 64.0). However, none of these changes were statistically significant.

The findings on weaner mortality and DWG are similar to the changes observed following the cessation of antimicrobial growth promoter use in Denmark and Sweden in the 1980s and 1990s. Here a significantly higher mortality in weaners was seen combined with a significantly lower weaner DWG (Wierup, 2001; Kjeldsen and Callesen, 2006). However for finishers, this study observed a trend towards a higher mortality and a lower DWG, whereas no similar difference was reported following the cessation of antimicrobial usage in either country (Robertsson and Lundeheim, 1994; Wierup, 2001; Kjeldsen and Callesen, 2006; Aarestrup et al., 2010). This may be due to the fact that this study only investigated herds with a marked decrease in antimicrobial consumption. The difference between changes in weaner and finisher parameters might be due a higher susceptibility in weaners to diseases and less tolerance to environmental stress factors - and therefore a higher risk of euthanization during disease outbreaks.

Prior to introduction of the yellow card initiative, the average weaner mortality in the study population (2.4%) was lower than the concurrent average national mortality (2.6%). However, following the introduction of the yellow card initiative, the average weaner mortality in the study population increased (3.1%) 0.2 percentage points above the concurrent average national weaner mortality (2.9%) (Jessen, 2015). Hence, the reduced antimicrobial usage might have been at the expense of a higher disease incidence and subsequent increased mortality rates. Furthermore, it was found that herds with a high weaner antimicrobial

consumption prior to the introduction of the yellow card initiative also experienced a larger increase in mortality following the reduction in antimicrobial consumption. This might suggest that these herds had a higher disease pressure and consequently suffered a larger increase in mortality, when the antimicrobial consumption was reduced. However, further studies are needed to discern the exact causes for the larger increase in mortality.

An attempt can be made to elucidate a long-term prognosis on mortality and DWG based on the different findings published in relation to cessation of antimicrobial growth promoter use. In a Swedish study following the ban on antimicrobial growth promoter use, weaner mortality had not yet reached its former low values ten years after (Wierup, 2001). However, despite a steadily increasing weaner mortality in the years immediately following the ban on antimicrobial growth promoters in the late 1990s, the Danish weaner mortality decreased steadily from 2004 to 2009 (Vinther, 2011). As a result of this decrease, Danish weaner mortality was at a lower level prior to the introduction of the yellow card initiative than before the cessation of antimicrobial growth promoter use (Aarestrup et al., 2010). Aarestrup's findings may indicate that an increase in mortality following introduction of restrictive legislation may level out over time due to advances in the pig production, such as improvements in breeding, housing and biosecurity.

4.6 LMP and lesions at slaughter

4.6.1 LMP

A significant increase in LMP at slaughter was observed following the introduction of the yellow card initiative. In a study published in 2011, Stege et al. stated that a high LMP may be reflective of a low DWG and vice versa (Stege et al., 2011). This is concurrent with the findings of this study, which, in addition to a statistically significant higher pig LMP, found a trend towards lower weaner and finisher DWG. However, despite a trend towards both higher weaner and finisher DWG standard deviation following the introduction of the yellow card initiative, LMP standard deviation decreased in the same time frame (4.4 to 4.2; $p=0.64$). This discrepancy might be caused by several factors leading to more uniform pigs at slaughter, such as an increased acceptance of a higher mortality leading herd managers to cull pigs at an earlier stage or improvements in day-to-day management. Furthermore, the discrepancy may also be due to the relatively different sub-populations, as the finisher DWG analyses were performed on data from 38 herds and LMP analyses on data from 75 herds.

For analysis of LMP, it would have been optimal to include the sex of slaughtered pigs as an independent variable in the model, as female pigs have been found to have higher LMP compared to males (Just and Pedersen, 1976; Latorre et al., 2003). Unfortunately, these data were not available to the authors at time of submission.

4.6.2 Lesions at slaughter

This study demonstrated a significant increase in the prevalence of tail bites, chronic peritonitis and abscesses in head and ears, respectively. The significant increase in abscesses in head and ears might be due

to an increase in injections of both antimicrobials and vaccines with subsequent injection injuries. However, more studies are needed to establish whether this is truly the case.

A significant decrease was observed in the prevalence of chronic pneumonia and chronic pleuritis. This might be coupled to the increased purchase of vaccines against respiratory diseases in the concurrent time period (Alban et al., 2013). No significant change in the prevalence of chronic pleuritis was found when performing a simple χ^2 -test ($p=0.33$). However when taking clustering of data into account, a significant decrease was found ($p<0.0001$). This may be explained by the large difference in prevalence between herds. Chronic pleuritis had the highest MOR for herd level at 19.88, meaning that a pig had almost 20 times higher odds of having chronic pleuritis at slaughter if moved from the herd with the lowest odds of disease to the herd with the highest odds of disease. No other lesion at slaughter had a herd MOR higher than 2. It must be remembered that this study unfortunately did not have access to data on which abattoir the pigs were slaughtered at, only that individual herds had not changed abattoir during the study period. Herd MOR might therefore also partly reflect the difference between abattoirs.

When including season and period in the analyses, no MOR higher than 2 was observed for any lesion at batch level. This may reflect an overall homogeneity between batches within herds. This would be in concordance with the original selection criteria that participating herds should have undergone no major changes in manage-

ment during the study period except for a decrease in antimicrobial consumption from period 1 to period 2.

Even though the prevalence of tail bites increased, the prevalence of infected tail bites at slaughter decreased. As stated by Alban et al. (2013) tail bites infection is a complex issue, where many factors are at play. Consequently, further studies are needed to investigate the exact cause of this difference.

The findings on OR for chronic pneumonia, chronic pleuritis, chronic peritonitis, chronic arthritis and tail bite infection are in line with those reported by Alban et al. (2013), who investigated the prevalence of select lesions at slaughter before and after the instigation of the yellow card initiative in all finisher pigs sent to one large Danish abattoir (1.7 million pigs). However, as opposed to the findings published by Alban et al., this study did not discern any significant increase in osteomyelitis or chronic enteritis following introduction of the yellow card initiative, despite a slightly increased odds ratio for both (osteomyelitis: 1.08; chronic enteritis: 1.01). This may be due to the relatively smaller sample size, demanding larger differences for a statistical significance to show.

5 Conclusions

An increased use of vaccines and less herd medication were the most factors most frequently stated as having contributed to the decrease in antimicrobial usage by both herd managers and veterinarians. On changes in productivity and health parameters following introduction of the yellow card initiative, weaner mortality was found

to have increased significantly and a trend towards a higher finisher mortality was observed. Furthermore, trends were seen towards both lower average weaner and finisher DWG and higher DWG standard deviation. LMP at slaughter increased significantly, however no significant change in LMP standard deviation was found. For lesions at slaughter a significant increase was seen in the prevalence of tail bites, chronic peritonitis and abscesses in head and ears, respectively. These findings suggest that lowering the antimicrobial consumption through punitive legislation might not be without productivity and consequently welfare related consequences on a short term basis. It may therefore be prudent to consider relevant biological context when designing antimicrobial restrictive legislation. In line with this, the Danish government has recently announced that the legislation surrounding the yellow card initiative may potentially be modified. The goal is to create a differentiated yellow card, where the value pinpointing a herd for a yellow card penalty will be decided by the type of antimicrobials used based on antibacterial spectrum and importance in human medicine.

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6 Discussion

6.1 Challenges encountered when using VetStat data to estimate pig antimicrobial usage

The first study centered on describing the present structure of VetStat. This knowledge was expanded on in paper I (part of study 2), which focused on delineating a select set of challenges encountered when attempting to use VetStat data to estimate actual herd level pig antimicrobial consumption and corresponding solutions.

As outlined in chapter 4.1.3, inconsistencies and errors in VetStat data especially occurred during the first few years following the implementation of VetStat. It is imperative to take such issues into consideration when analyzing VetStat data. Failing to do so might lead to false conclusions, such as potential erroneous estimations on trends in antimicrobial usage. An increase in antimicrobial consumption according to Vetstat data from the early years might not reflect a true increase in consumption, but rather an increase in the registration of data. The initial difficulties of VetStat are in agreement with a statement from the European Medicines Agency, who in the fifth ESVAC report stated: *“It is generally agreed that it takes at least three to four years in order to establish a valid baseline for the data on sales of veterinary antimicrobial agents. Consequently, the data from countries that have collected such data for the first or even second time should be interpreted with due caution”* (European Medicines Agency, 2015d). However, not only time but also the implementation of new legislations may alter the validity of data as was seen in relation to the amount of entries on pig antimicrobial consumption with invalid age group, which from 0.5% in 2009 to 0.02% in 2011.

Even when working with sales data submitted in later years, it is still essential to clean, check and validate data (Emanuelson and Egenvall, 2014). Sales data extracted for the same time period, but at different time points, may contain different data due to e.g. transfer fails, recent updates or manual corrections in sales data performed by DVFA employees. Data in supplementary VetStat tables must also be assessed before use. As an example, all products' individual ADD-values are manually entered into a VetStat supplementary table containing information on dosage per kg live animal. Consequently, this sets the scene for potential erroneous data due to typing errors or other human mistakes, even though errors are corrected immediately when discovered by DVFA employees.

Aside from challenges related to data validity, other difficulties can mainly be divided into two groups. Firstly, there is the type of challenges arising from the fact that practicality has sometimes prevailed over data detail level, such as (i) Vetstat data being sales data from medicine distributors (pharmacies/feed mills/veterinary practitioners) and not end-user data from farmers; or (ii) the fact that pre-weaning pigs are pooled together with sows, breeding gilts and boars in one age group at a 200 kg standard weight instead of allocated to separate age groups. Secondly, there is the type of challenges that occur when attempting to use VetStat data for something it was not originally intended for. An example of this could be seen in the immediate period following introduction of the yellow card initiative, when a number of farmers received a yellow card warning letter due to errors in VetStat data (Danish Veterinary and Food Administration, 2014), as no automatic logical check exist for discrepancies between the registered animal species and age group.

To complicate matters for researchers working with VetStat data, no logs are presently publicly available on changes in the database structure, data management processes or on any retrospective changes in sales data performed by DVFA employees. According to DVFA employees, retrospective corrections in sales data are seldom needed nowadays (E. Jacobsen, personal communication). However, the inaccessibility to logs on such retrospective changes in sales data makes it difficult for outside researchers to adjust for these potential corrections.

Despite the challenges encountered when using secondary data, Vetstat represents a unique data source for researchers working with surveillance of veterinary medicine consumption. Vetstat data are cheaper and easier to obtain compared to the collection of primary data. Additionally, VetStat data have national coverage for an extended time period and are at present the secondary information closest to data on actual consumption. Alternative to VetStat data, antimicrobial usage could be estimated based on registrations by farmers. This might give a better indication of the actual usage. However, farmers' registrations have also been found to be subject to missing (Merle et al., 2012) or potentially erroneous data, such as wrong product name, dosages differing from those stated by the veterinarian or implausible combinations of age and disease groups, such as mastitis in pre-weaned pigs (Chauvin et al., 2005; González et al., 2010; Trauffler et al., 2014). In addition, studies based on data submitted by farmers often rely on voluntary participation (Dunlop et al., 1998; Sawant et al., 2005; González et al., 2010; Moreno, 2012) increasing the risk of selection and participation bias.

The findings of study 1 and 2 highlight the need to critically assess the validity and appropriateness of using the secondary data in question prior to application. This is in concurrence with previous publications on secondary data use (Schneeweiss and Avorn, 2005; Harpe, 2009). Based on the findings of this PhD, it is strongly recommended to investigate the opportunities and limitations of VetStat data prior to the actual application in research.

6.2 Deciding challenges and solutions as group (paper I)

Paper I is the result of a collective wish to share knowledge and experience on working with VetStat data. The wish was formed by an interinstitutional group of researchers working intimately with VetStat data. The interacting group method (Van de Ven and Delbecq, 1974) was chosen to decide which challenges should be included and to define said challenges and their corresponding solutions. The interacting group method was chosen for several reasons. Firstly, it was deemed that discussions between panel members would benefit the presented results. To reach a consensus on the importance of each challenge and the stability and usefulness of suggested solutions, each researcher had to explain and justify his or her statements to the group at large. Secondly, the group had already met physically prior to formation of the paper and exchanged knowledge on VetStat data. Any independent statements from panel members would therefore unavoidably be influenced by knowledge exchanged at previous meetings.

Due to the interactive nature of the meetings, all challenges and solutions presented in paper II are a result of the collective experience of all panel members with all panel members being influenced by one another's input (Fay et al., 2000). Consequently, a differently composed panel with other VetStat data experiences would most likely have suggested a different set of challenges and equally different solutions.

6.3 Influence of assigned daily dosage values and population measurement in relation to estimation of national pig antimicrobial usage

Paper II (second part of study 2) focused on investigating how assigned ADD-values and population measurement influenced the calculated national pig antimicrobial consumption with a specific emphasis on trend over time. The study was performed as a retrospective database study investigating Denmark's national pig antimicrobial consumption from 2007 to 2013 based on three sets of ADD-values and four different population measurements.

Both chosen set of ADD-values and chosen population measurement were found to highly influence the calculated annual pig antimicrobial consumption. As an example, annual antimicrobial consumption per produced pig in 2013 was found to be 23% higher when calculated with the DVFA ADD-values, compared to the consumption calculated with the VetStat ADD-values. Differences in trend over time were also observed. From 2007 to 2013, the antimicrobial usage in number of ADDs/pig/year increased by 22% when calculated with pigs slaughtered per year as population measurement and the DVFA ADD-values. However, when using pigs produced per year and the VetStat ADD-values, the annual antimicrobial usage per pig had decreased by 11%. In addition to underlining how sensitive evaluation of trends in antimicrobial consumption is to calculation method, this also underlines the need to ensure that only numbers achieved through the same calculation method are compared di-

rectly, when wishing to evaluate trends over years. The finding that chosen set of ADD-values highly affect the calculated results is in agreement with a study by Taverne et al., who investigated the Dutch pig antimicrobial usage in 2012 using three different sets of ADD-values (Taverne et al., 2015).

It is recommended that researchers carefully choose the set of ADD-values most appropriate to their specific research question. If e.g. a researcher wishes to investigate whether a farmer perceived him or herself as a high consumer of antimicrobials in 2012, the VetStat ADD-values should be applied, as these were used in 2012 to calculate the numbers presented in the herds' individual consumption graphs in relation to the yellow card initiative, available to each farmer on the VetStat website.

The shift in ADD-values, from being based on information in each product's Summary of Product Characteristics (SPC) to solely being based on actual product content, occurred following the introduction of the yellow card initiative. At the instigation of the yellow card initiative, ADD-values were primarily SPC-based. Consequently, some products had differing ADD-values, despite containing identical active ingredients, strengths and both being approved for the same administration route (DANMAP, 2012a). This hampered estimates of the true antimicrobial exposure, as a shift from one product to another with identical content but a different approved SPC dosage value could highly affect calculated results. Consequently, a new method of assigning ADD-values had to be developed. The Danish experience on ADD-values is highly relevant in an international context. In Europe, work is presently being put towards developing a common set of ADD-values to enable comparisons between countries. In 2014, the MINAPIG consortium (www.minapig.eu) released a paper on a common set of ADD-values for four European countries (Postma et al., 2014) and as previously mentioned in chapter 2.1.3, ESVAC is presently developing its own set of ADD-values intended for use in the ESVAC reports on veterinary antimicrobial usage in EU member states (European Medicines Agency, 2015b). On a long-term perspective, the ESVAC set of ADD-values has also been thought to potentially fill the same function as the WHO DDD-values by supplying a uniform method of quantifying veterinary antimicrobial usage accessible to all researchers (European Medicines Agency, 2015a).

According to the newest report released in 2015, ESVAC ADD-values will be based on product SPCs (European Medicines Agency, 2015b). In the commentary report on the ESVAC ADD-values, the Veterinary Medicines Directorate from the United Kingdom briefly mentions that using SPCs to decide ADD-values may bias results, if a specific subgroup of producers choose to use products with a lower SPC dose. However, the commentator does not deem this a major issue, as she/he states that this problem would only be relevant in countries using the ADD-values "*for enforcement purposes at farm or sector level*" (European Medicines Agency, 2015a). However, even though not based on the ESVAC ADD-values such enforcements are already in place in Denmark, the Netherlands and Belgium based on each country's own set of ADD-values (Alban et al., 2013; Bos et al., 2013; De Graef, 2014). Based on the findings of paper II, it is highly recommended that due consideration is given

before SPCs are used as a basis for product ADD-values, as a preference for some products over similar competing products may highly affect calculated results, be it at farm, region or country level. Furthermore, in the current political climate, other countries may decide to instigate legislation similar to the Danish yellow card initiative and will consequently at some point find themselves in the same situation potentially having to change ADD-values, if these have been SPC-based previously, as they presently are in e.g. the Netherlands (Bos et al., 2013).

Regardless of whether ADD-values are based on SPCs or content, it is essential to remember that ADD is a technical unit and as such does not necessarily reflect actual number of used doses (Jensen et al., 2004; European Medicines Agency, 2015b). This divergence has been shown in three Belgian studies investigating antimicrobial usage in both herds producing veal calves (Pardon et al., 2012) and fattening pig herds (Timmerman et al., 2006; Callens et al., 2012) and in an Austrian study performed in conventional pig herds (Trauffler et al., 2014). In the three Belgian studies, the consumption was found to be higher when calculated in ADD compared to the actual number of used daily doses. Whereas in the Austrian study, the calculated antimicrobial consumption was found to be lower when reported in ADD compared to number of used daily doses, emphasizing the need to interpret findings in ADD with caution. An argument can be made that since these studies were performed abroad, they cannot be used to make inferences on Danish consumption patterns. However, in a Danish pilot study from 2004 a Danish swine veterinarian was asked to provide doses for 51 antimicrobial drugs. Here it was found that in 20% of the investigated antimicrobial products, prescribed daily dose deviated >10% from the product's stated ADD-value (Jensen et al., 2004). Where the prescribed daily dose deviates from the ADD, it can be assumed that the used daily dose also deviates from the ADD. Consequently, there is a need to inform readers of research on antimicrobial consumption that deviations between ADD and used daily doses exist. However, without extensive in-depth studies the exact magnitude of this difference is difficult to assess precisely.

In addition to ADD-values, chosen population measurement was also found to highly influence the calculated antimicrobial consumption. From 2007 to 2013, the overall Danish pig production increased. However, while number of pigs exported live increased, number of pigs slaughtered nationally decreased. It is therefore not surprising that the calculated annual consumption per slaughtered pig is higher for all years from 2007 to 2013 compared to the consumption per produced pig (including live exported pigs), with the overall difference increasing over time. As an example, the antimicrobial consumption in 2007 was 14.6% higher when pigs slaughtered in Denmark was used as a population measurement (13.0 ADDs/pig slaughtered/year; DVFA ADD-values) compared to the consumption calculated based on pigs produced, including the live export (11.1 ADDs/pig /year; DVFA ADD-values). In 2013, this difference had increased to 27.0% (15.9 ADDs/pig slaughtered in DK/year versus 11.6 ADDs/pig produced/year). This clearly highlight the importance of taking animal demographics into consideration, when calculating antimicrobial consumption, which is in agreement with previously published scientific papers by Grave et al. et Bondt et al. (Grave et

al., 2010; Bondt et al., 2013). In countries such as Denmark with a substantial pig export, erroneous conclusions may ensue if live exported 30 kg pigs are not taken into account when estimating antimicrobial consumption per produced pig. Not including 30 kg pigs may skew results markedly, as weaners from 2007 to 2012 accounted for 77-79% of the total Danish pig antimicrobial consumption in ADDs (DANMAP, 2012c).

6.4 Factors contributing to reduce antimicrobial usage following introduction of the yellow card initiative

In the first part of study 3 (part of paper III), it was found that both high and low consumer herds had decreased their antimicrobial usage following the introduction of the yellow card initiative. This decrease in antimicrobial usage regardless of prior antimicrobial usage may be related to the threat of potential financial repercussions. This would correspond with previous studies, where financial incentive has been reported as one of the farmers' primary motivators when choosing to implement new management or bio-security procedures (Gunn et al., 2008; Fraser et al., 2010; Valeeva et al., 2011; Laanen et al., 2014; Speksnijder et al., 2015a). Another identified incentive to implement new disease control initiatives is increased mortality (Alarcon et al., 2014). However, some herd managers may decide that a higher mortality is acceptable in order to reduce the antimicrobial consumption sufficiently. In this study, seven herd managers explicitly stated in the questionnaire that besides from their other implemented initiatives they had also started to cull diseased pigs earlier, accepting a higher mortality rate to lower their antimicrobial consumption.

In general, most of the stated antimicrobial reducing initiatives, such as vaccines, staff education, change in feed and increased focus on cleaning procedures, could be implemented in a relatively short time span and without major financial investments. In addition to vaccines and improved management (Arnold et al., 2004; Laine et al., 2004; Postma et al., 2015), external facilities have also been stated as a factor when attempting to reduce antimicrobial usage without productivity losses (Wierup, 2001; Fortané et al., 2015). However, costly initiatives, such as reinvestment in buildings and farm infrastructure, may be beyond the financial capacity of the majority of pig producers in the present economic climate (Alarcon et al., 2014; Speksnijder et al., 2015b). These financial impediments may leave farmers reluctant towards lowering their antimicrobial usage, if they assess that antimicrobials are essential to stem production costs (Coyné et al., 2014).

Shorter treatments were stated by 17% and smaller dosages by 14% of the farmers, as having aided in reducing antimicrobial usage. Further studies are needed to discern whether the treatment regimens currently applied are now in line with veterinary recommendations, as sub-therapeutic levels may increase the risk of developing antimicrobial resistance (Olofsson and Cars, 2007).

6.5 Reliability and validity of information collected through phone interviews and questionnaires

Reliability of information collected in the questionnaire was investigated with the test-retest method in a pilot group. Furthermore, all herds were asked twice whether any changes in animals at stable had occurred, once in an initial telephone interview and once in the questionnaire. However, an estimate of reliability does not qualify any assessments on the validity of the given information, as a statement is not necessarily more correct simply because it has been stated several times (Dex, 1995). It would have been optimal to verify the validity of answers through e.g. a pilot study. This, especially as an increasing temporal gap between actual event and prompt for recall is known to exacerbate the risk of failing to recollect the actual event or mistaking its date of occurrence (Coughlin, 1990). Unfortunately this was not possible due to time constraints.

As with any questionnaire, a risk exists that respondents were not representative for the intended target population (Asch et al., 1997), especially as there have been indications that non-response is not arbitrary (van der Zouwen and de Leeuw, 1995). Minimal response rates recommended vary greatly from 50% to 80% (Sackett, 1979; Baruch and Holtom, 2008). This study had a non-response rate of 16.7% of all the initially randomly selected herds, which reduces the inherent risk of non-representativeness caused by non-respondents. No obvious differences were identified between non-respondents' and respondents' antimicrobial usage patterns (level prior to the introduction of the yellow card initiative and as decrease in %).

During study III, an interesting finding was made in relation to whether a change in number of animals at stable had occurred. At the beginning of the study, only CHR data on number of animals on 31 December 2010 were available. It was therefore not possible to validate the farmers' responses with CHR data. However, at a later time point new data extractions from the CHR database became available on the number of animals in each herd according to age species on 31 December 2009 and 2011. Consequently, it was now possible to validate the herd managers' responses with CHR data. Herds were then contacted by phone, whenever there was incongruity between their response and the CHR data with regards to change in number of animals at stable. This was done to determine when the actual change in number of animals had taken place. Firstly, it was possible that the change in number of animals at stable had occurred after the end of the investigated study period as data were only available on number of animals on 31 December 2009, 2010 and 2011. Secondly, some delay may exist between actual change in number of animals at stable and number of animals registered in CHR. At contact, a few herd owners stated that they had changed the number of pigs in CHR prior to the actual change in number of pigs at stable. These herds were consequently not excluded from the study. This underlines the challenge of attempting to estimate antimicrobial exposure based on database extractions, which was briefly mentioned in the paper "Vetstat-paper". The potential delay between actual change in number of pigs and update of CHR data or vice versa, may lead to faulty estimations on consumptions during periods

where the two are not perfectly aligned. However, investigating the extent of this type of discrepancy was beyond the scope of this PhD thesis.

6.6 Changes in mortality, daily weight gain, lean meat percent and lesions at slaughter following introduction of the yellow card initiative

6.6.1 Changes in mortality and daily weight gain

Following introduction of the yellow card initiative, weaner mortality was found to increase significantly from 2.4% to 3.1% ($p=0.0001$). Additionally, a trend was seen towards a lower weaner average daily weight gain and a higher standard deviation in weaner daily weight gain. The fact that no significant changes in daily weight gain parameters were identified may be due to the relatively small number of weaner-producing herds included in the final analyses (43 herds), compared to the number of herds needed according to the initial sample size calculation (79 herds). On an overall national scale, weaner mortality increased from 2.6% to 2.9% and average weaner daily weight gain decreased from 460 to 443 grams per day between 2009 and 2011 (Jessen, 2015). It is of interest to note that prior to introduction of the yellow card initiative, the average weaner mortality in the study population (2.4%) was lower than the concurrent average national mortality in 2009 (2.6%). However, following introduction of the yellow card initiative, the average weaner mortality in the study population (3.1%) increased to 0.2 percentage points above the concurrent average national weaner mortality in 2011 (2.9%) (Jessen, 2015). For finisher herds participating in the study, trends were observed towards a higher mortality (3.3% to 3.7%; $p=0.51$), a lower average daily weight gain (890 to 867 grams per day; $p=0.71$) and a higher average daily weight gain standard deviation (58.8 to 64.0; $p=0.43$). This is in contrast to the national finisher averages, where mortality decreased from 4.1% to 3.7% and average daily weight gain remained unchanged (898 grams per day) from 2009 to 2011 (Vinther, 2014).

These findings may suggest that the reduction in antimicrobial usage might have been at the expense of higher disease incidences and subsequent increased mortality rates. This is supported by the finding that herds with a high weaner antimicrobial consumption prior to the introduction of the yellow card initiative also experienced a larger increase in mortality following the reduction in antimicrobial consumption. However, supplementary studies are recommended to further elucidate the exact causes for this study population's larger increase in mortality compared to the overall Danish pig population.

Data on mortality and daily weight gain were collected as IT-based production reports. In the reports, mortality and daily weight gain are based on number of pigs entering the stable,

number of pigs leaving the stable, weight at entry and weight at exit. To adjust for the differing time intervals of the submitted production reports, mortality and daily weight gain averages were calculated as weighted averages as described in paper III – chapter 2.5.1 “*Analyses of mortality and DWG*”. This was done, as the numbers stated in the production reports are based on sums of numbers over an entire period and not based on a measurement at a single date. Consequently, a repeated analysis was not performed as the model would have assumed that each observation was a point in time and not, as it was actually the case, a value which covered an interval in time. An alternative to the production reports as a data source would have been to conduct several herd visits to collect information on pig weight and mortality. However, as the study was performed retrospectively it was deemed most feasible to use the already collected data. If one was to calculate sample sizes based on the findings of this study, data from 167 herds would be needed to analyze finisher mortality, assuming data was paired according to herd. If investigating change in finisher daily weight gain, data would be needed from 3232 herds (both calculated with PROC POWER, SAS Enterprise 7.1; power: 0.8; α : 0.05).

Initially, information was gathered on the official health status of the herds according to the Danish Specific Pathogen Free (SPF)-system (Thomsen et al., 1992) with the aim to investigate if herd health status affected a potential change in productivity and health parameters. However, SPF-status was excluded from the final analyses, as: (i) several finisher herd owners knew their herds to be free from several of the diseases monitored in the SPF-system, but were not enrolled in the SPF-system due to financial reasons; and (ii) a sufficient amount of data from different herds had not been gathered to justify a further stratification (splitting up) of herds into subgroups.

The findings of this study on mortality and daily weight gain are similar to the changes observed following the cessation of antimicrobial growth promoter use in Denmark and Sweden in the 1980s and 1990s. Here, both significantly higher weaner mortalities and lower weaner daily weight gains were seen with no significant changes in finisher mortality or daily weight gain (Robertsson and Lundeheim, 1994; Wierup, 2001; Kjeldsen and Callesen, 2006; Aarestrup et al., 2010). Earlier studies have especially attributed the negative impact on productivity to a rise in diarrhea (Vigre et al., 2008) with specific emphasis on post weaning diarrhea (Wierup, 2001; World Health Organization, 2002). Consequently, the difference between changes in weaner and finisher parameters might be due to weaners having a higher susceptibility to enteric diseases and a lower tolerance to environmental stress factors (Hopwood and Hampson, 2003; Stein and Kil, 2006) leading to a greater risk of needing treatment (van Rennings et al., 2015) or requiring euthanization during a disease outbreak.

A Finnish study reported no negative impact on productivity following cessation of antimicrobial growth promoters (Laine et al., 2004). However, Laine et al. only investigated changes in: (i) number of piglets weaned/sow/year, (ii) age at weaning, (iii) mortality from live birth to weaning, (iv) perceived frequency of diarrhea according to farm advisors and (v) level of antimicrobial usage to treat weaner diarrhea (low/moderate/high) (29 herds). The study did not include any investigations of productivity parameters following weaning, such as mortality,

daily weight gain or feed conversion rate. Additionally, the Finnish study was performed in a relatively smaller study population (73 herds) compared to the Danish (1,500 herds) and Swedish (220 herds) studies (Wierup, 2001; Kjeldsen and Callesen, 2006)

An attempt can be made to elucidate a long-term prognosis on mortality and daily weight gain based on the different findings published in relation to cessation of antimicrobial growth promoter use. In a Swedish study, weaner mortality had not yet reached its former low values ten years after the ban on antimicrobial growth promoter use was implemented (Wierup, 2001). However, despite a steady increase in the Danish weaner mortality in the years immediately following the ban on antimicrobial growth promoters in the late 1990s, overall weaner mortality decreased steadily from 2004 onwards (Vinther, 2011). As a result of this decrease, Danish weaner mortality was at a lower level prior to the introduction of the yellow card initiative than before the cessation of antimicrobial growth promoter use (Aarestrup et al., 2010). The findings by Aarestrup et al. may indicate that an increase in mortality following introduction of restrictive legislation may level out over time due to advances in the pig production, such as improvements in breeding, housing and biosecurity.

6.6.2 Lean meat percent at slaughter

A significant increase in lean meat percent at slaughter was observed following the introduction of the yellow card initiative (60.05 to 60.18; $p < 0.0001$). In a study published in 2011, Stege et al. stated that a high lean meat percent may be reflective of a low daily weight gain and vice versa (Stege et al., 2011). This is in concurrence with the findings of this study, which both identified a significantly higher pig lean meat percent and trends towards lower weaner and finisher average daily weight gain. However, despite an increase in the standard deviation of both weaner and finisher daily weight gain, standard deviation of lean meat percent was found to decrease in the same time interval (4.4 to 4.2; $p = 0.64$). This discrepancy may be due to the relatively different sub-populations, as analyses on finisher daily weight gain were performed on data from 38 herds, whereas analyses on lean meat percent were performed on data from a relatively larger population of 75 herds. Furthermore, the discrepancy might also be caused by several factors leading to more uniform pigs at slaughter, such as an increased acceptance of a higher mortality leading herd managers to cull pigs at an earlier stage or improvements in day-to-day management. However, further studies are needed to elucidate whether this is actually the case.

For analysis of lean meat percent, it would have been optimal to include the sex of slaughtered pigs as an independent variable in the model, as female pigs have been found to have higher lean meat percent compared to castrated males (Just and Pedersen, 1976; Latorre et al., 2003). Unfortunately, these data were not available to the authors at time of submission.

6.6.3 Lesions at slaughter

This study demonstrated a significant increase in the prevalence of tail bites, chronic peritonitis and abscesses in head and ears. The significant increase in abscesses in head and ears might be due to an increase in injections of both antimicrobials and vaccines with subsequent injection injuries. However, more studies are needed to establish whether this is truly the case. A significant decrease was observed in the prevalence of chronic pneumonia and pleuritis. This might be coupled to the increased purchase of vaccines with an effect on respiratory diseases in the concurrent time period (Alban et al., 2013). No significant change in the prevalence of chronic pleuritis was found when performing a simple χ^2 -test ($p=0.33$). However, a significant decrease was found when taking the clustered nature of data (herd, batch) into account ($p<0.0001$). This may be explained by the large difference in prevalence between herds. Chronic pleuritis had the highest herd MOR at 19.88, meaning that a pig had almost 20 times higher odds of having chronic pleuritis at slaughter if moved from the herd with the lowest odds of disease to the herd with the highest odds of disease. No other lesion at slaughter had a herd MOR higher than 2. It must be remembered that this study unfortunately did not have access to data on which abattoir the pigs were slaughtered at, only that individual herds had not changed abattoir during the study period. Herd MOR might therefore also reflect the difference between abattoirs.

When including season and period in the analyses, no MOR higher than 2 was observed for any lesion at batch level. This may reflect an overall homogeneity between batches within herds. This would be in concordance with the original selection criteria, that participating herds should have undergone no major changes in management during the study period except for a decrease in antimicrobial consumption from period 1 to period 2.

The findings on OR for chronic pneumonia, chronic pleuritis, chronic peritonitis, chronic arthritis and tail bite infection are in line with those reported by Alban et al. (2013), who investigated the prevalence of select lesions at slaughter before and after the instigation of the yellow card initiative in all finisher pigs sent to one large Danish abattoir (1.7 million pigs). However, as opposed to the findings published by Alban et al., this study did not discern any significant increase in osteomyelitis and chronic enteritis following the introduction of the yellow card initiative found in this study, despite a slightly increased odds ratio for both. This may be due to the relatively smaller sample size, demanding a larger difference for statistical significance to show.

Data on lean meat percent and lesions at slaughter were registered by educated staff at the abattoirs (Alban et al., 2013). However, sensitivity and specificity for detection and classification of lesions at slaughter may differ between abattoirs (Enøe et al., 2003; Denwood et al., 2015) and between individual staff members (Bonde et al., 2010). To minimize effect of abattoir, herds were excluded if they had changed abattoir at any time point throughout the entire study period. Unfortunately, it was not possible to adjust for individual observer, as data on observer were not available. A conservative p-value ($p=0.01$) for analyses of lesions at slaughter was chosen in an attempt to minimize the risk of faulty conclusions and to take precautions for the large quantity of observations. However, conclusions on lesions with a low

prevalence must still be interpreted cautiously, as these are more sensitive to inter- and intra-observer variation. If it had been possible in this study to obtain data on the specific abattoir each herd had sent pigs to, a model could have been made which also accounted for clustering according to abattoir. Consequently, it is recommended that information on exact abattoir are collected whenever possible, if similar studies are to be carried out in the future.

6.7 Estimation of pig antimicrobial usage based on VetStat data

Both the second part of study 2 (paper II) and study 3 (paper III) were performed as retrospective studies using secondary data from VetStat to estimate antimicrobial usage. Many of the difficulties encountered when using VetStat data to assess antimicrobial usage have been described in detail in paper I. However, no other paper has to the author's knowledge yet been published on the challenges encountered when attempting to estimate antimicrobial usage based on data from national veterinary sales databases. Contrary to this, several studies have described the challenges encountered when using secondary data to estimate medicine consumption within the field of human medicine (Schneeweiss and Avorn, 2005; Harpe, 2009; Hoffmann, 2009). This difference may be due to the relatively larger number of pharmaco-epidemiologic publications based on human claims and prescription reimbursement databases compared to the corresponding number of veterinary publications. Just based on data from the Danish, Swedish, Finnish, Norwegian and Icelandic databases, 515 pharmaco-epidemiologic studies were published from 2005 to 2010 (Wettermark et al., 2013). Previous publications on validity of sales or claims data as a proxy for human medicine exposure have centred on the issues of (i) whether a purchased drug was actually consumed by the patient (Morris and Schulz, 1992; Sørensen et al., 2001; Kildemoes et al., 2011); or (ii) whether patients had obtained their drugs from an entity, which did not register sales in the assessed database – e.g. from foreign internet pharmacies, helpful relatives or medicine from a previous disease event (Strom, 2001; Wettermark et al., 2007; Polinski et al., 2009).

When one attempts to use publications from the field of human medicine to assess potential validity issues regarding veterinary medicine sales data, it is important to keep in mind that while sales of medicine for human patients are registered at individual level (Kildemoes et al., 2011), veterinary antimicrobial sales for production animals are only registered at age group and herd level (Stege et al., 2003). Consequently, it is easier to assess the actual antimicrobial exposure of an individual within human pharmaco-epidemiology (Grymonpre et al., 2006) than within veterinary pharmaco-epidemiology, as the exact identities of the individual treated pigs are not known when using VetStat data. Consequently, it is difficult for veterinary researchers to assess actual antimicrobial exposure within smaller groupings, such as pigs born within a specific week or pigs recently moved to a new stable section.

Paper II only focused on the overall national antimicrobial consumption per year. Consequently, any small differences in antimicrobial exposure within herds impacted results minimally. However, it is possible that an unknown amount of the overall amount of national antimicrobials sold in December was used at a later date in the following year. This might potentially lead to an underestimation of the consumption in the first months of the year. However, as paper II only investigated national consumption, it may be assumed that the lag time between time of sale and time of use generally remained stable throughout the study period for the overall consumption (2007-2013), thereby minimizing any potential effects on study conclusions.

Paper III estimated antimicrobial usage at herd level comparing consumption in consecutive years (1 June 2009-31 May 2010 to 1 June 2010 to 31 May 2011). Lag time between date of sale and date of use for single purchases may consequently have had a larger impact on the calculated herd antimicrobial usage in the investigated age group than on the estimation of the overall national consumption. Additionally, antimicrobials registered for use in another age group than the one actually treated may also have compromised calculated results on antimicrobial consumption. To correct for this, a more in-depth investigation would have been needed into the antimicrobial usage of each herd. This would e.g. have entailed data collection from each herd's antimicrobial treatment sheets which farmers are required by law to keep for a minimum of five years after a treatment is initiated (Anonymous, 2015a). However, no requirements are made as to how the records are stored, resulting in greatly varying degrees of ease of access and readability (G. Blach Nielsen, personal communication). Consequently, this method was not chosen due to project time constraints.

Validity of data on quantity and type of antimicrobial product purchased was deemed high in both paper II and III, as nearly all antimicrobials sold for use in pigs are registered by the pharmacies. Pharmacy entries are linked to the billing system. This minimizes the risk of an error going undetected, as the cost would be altered on the farmer's invoice. Furthermore, nearly all large pharmacies register type of product by scanning of a barcode, thereby removing the risk of typing errors. However, potential IT-based problems in the software of the pharmacies or VetStat may still give rise to errors in product type.

7 Conclusions

VetStat data present a rare opportunity to closely monitor pig antimicrobial usage at both national and herd level. However, when interpreting VetStat data it is essential to keep in mind that VetStat data are sales data and not actual usage data. Therefore the responsibility rests with the individual researcher to take the necessary precautions to avoid faulty conclusions. These include, but are not limited to, careful consideration of VetStat's data content, database structure and procedures in relation to each specific study hypothesis. While VetStat data submitted by pharmacies generally have a high degree of completeness and validity with regards to the quantity and type sold, errors may occur at all levels. Prudent vigilance is therefore advisable for all users of VetStat data. If data seem strange, an inquiry into the exact cause may be warranted.

The results presented in paper II clearly illustrate that choice of ADD-values and population measurement highly affects the calculated antimicrobial consumption, both when viewed as a single point in time and when evaluating trend over time. This underlines the need to always disclose a detailed description of calculation method when reporting antimicrobial usage. Furthermore, the results of the study demonstrate that demographics of a chosen population should always be considered carefully prior to analysis.

Increased use of vaccines, less herd medication and staff education were the factors most frequently stated to have facilitated the reduction of herd antimicrobial consumption. In herds that notably reduced their antimicrobial consumption, a significant increase in weaner mortality was observed following the introduction of the yellow card initiative. A trend towards a higher finisher mortality was also observed. Additionally, trends were observed for both weaners and finishers towards a lower average daily weight gain and a higher daily weight gain standard deviation. For findings at slaughter, lean meat percent was found to have increased significantly. No unambiguous overall result was identified regarding changes in prevalence of the investigated thirteen different types of lesions at slaughter. A significant increase was seen in the prevalence of localized tail bites, chronic peritonitis and abscesses in heads and ears. Conversely, chronic pleuritis, abscesses in front- mid- and rear section, chronic pneumonia, abscesses in feet and legs and infected tail bites all decreased significantly.

8 Perspectives

Study 1 and study 2 of this PhD thesis provide researchers new to VetStat with a base understanding of VetStat data, serving to minimize the risk of misinterpretation of data. Both studies are also of relevance to researchers, who seek deeper insight into the intricacies of working with data from a large national database on veterinary medicine sales. Institutions that are contemplating the implementation of databases similar to VetStat are advised to give due consideration to the expected purpose of their data, so construct of the data collected (e.g. groupings according to age), database structure and procedures can be designed accordingly. If possible, a high degree of transparency for all stakeholders should be aimed for to mitigate the risk of faulty conclusions. Furthermore, potential long-term ramifications should be considered, including consequences on a more personal level for both farmers and veterinarians, as highly personal information may become publicly available. One such situation has arisen in Denmark, where extensive lists on e.g. herds with a high antimicrobial consumption, including the name and address of the herd owner, have been published online (<https://sickpigs.dk>).

The presented results in paper II clearly illustrate how dramatically chosen calculation method can affect the calculated consumption. This imparts researchers and governmental institutions with a responsibility to clearly communicate that ADD is a technical unit, which must consequently be interpreted with caution. Especially researchers, journalists, politicians and other stakeholders, to whom results are presented in ADD per pig, should be made aware of this circumstance. It is therefore essential that calculation routines are disclosed comprehensively to ensure transparency. Based on knowledge obtained through an extensive literature study and the findings of paper II, it is furthermore recommended that choice of measurement unit and choice of denominator (population) are decided based on the aim of the individual study when wishing to report antimicrobial usage. Paper II is also relevant to all institutions considering how to best define ADD-values, as these may need to be altered at a later date if bench-mark legislation similar to the yellow card initiative is implemented, where SPCs have been chosen as the sole foundation.

Last but not least are the results of study 3. Researchers, farmers and veterinarians may share an interest in knowing how the reduction in antimicrobial usage following the introduction of the yellow card initiative was achieved according to the participating farmers and veterinarians, supplementing studies on how antimicrobial reduction has been achieved in other countries (Fortané et al., 2015; Speksnijder et al., 2015b). Furthermore, the productivity and health changes observed in herds with a marked decrease in antimicrobial consumption following

introduction of the yellow card initiative will likely be of interest to the majority of stakeholders involved in the effort to reduce veterinary antimicrobial usage.

National antimicrobial reduction initiatives are often furthered by public debates with subsequent political agendas to reduce the occurrence of antimicrobial resistant pathogens by curbing the veterinary antimicrobial usage (Alban et al., 2013; Fortané et al., 2015; Speksnijder et al., 2015b). In Denmark, the yellow card initiative was implemented with the political goal to reduce the animal production's antimicrobial usage by 10% over a three year period (Petersen and Larsen, 2010). The threshold values have so far been defined politically on the premise that 5-10% of the Danish pig herds should be above the new threshold value, when it is decided. However, in light of the findings of study 3, it may be recommended to base future threshold values on biological parameters rather than solely on statistics. Concordantly, the Danish government is presently working in collaboration with pig industry stakeholders to develop a differentiated yellow card legislation. If the legislation is passed, it will mark a departure from the current praxis of pinpointing high consumer herds based on an overall measurement of consumption and the updated legislation will potentially see penalties issued on basis of the type of antimicrobials used determined by antimicrobial spectrum and importance in human medicine.

A key motivation for implementing restrictions on antimicrobial usage at a national level is to curb the development of antimicrobial resistance. However, the Danish pig production should not be regarded simply as an isolated entity. With the increasing globalization it would be a major fault to disregard the potential travel of antimicrobial resistant pathogens across national borders. In recent years, the occurrence and spread of antimicrobial resistance and veterinary antimicrobial usage, have gathered rising attention internationally. This has resulted in large cross-national initiatives, such as the MINAPIG-project (Stärk et al., 2012), the European expert group on collection and analysis of veterinary antimicrobial consumption aiming to share experiences and knowledge on antimicrobial reporting and the EFFORT-project (EFFORT, 2016). Consequently, the field of knowledge within antimicrobial consumption surveillance is continually expanding.

Future recommended studies

Future recommended studies include:

- I. A study comparing calculated weaner antimicrobial consumption (ADD/100 animals/day) between herds with both weaners and finishers and herds with only weaners registered in the herd in CHR. This, as a farmer with finishers will potentially have the opportunity to register medicine purchased for a disease outbreak in large weaner pigs (e.g. 29 kg) for finishers), thereby getting a lower antimicrobial consumption on paper when calculated in ADD.
- II. An elaboration on the findings in paper III, investigating additional production parameters, such as feed conversion rate, and long term consequences.

- III. Investigation into the present dosing schemes in herds, which have reduced their antimicrobial consumption following introduction of the yellow card initiative. The amount of farmers who now use smaller dosages or shorter time intervals may be lower than estimated in this study, as it has previously been identified that respondents may underreport, if they believe the answer to be socially undesirable (Coughlin, 1990).

In addition, a call is made for an investigation into the validity of VetStat data when used as a proxy for actual antimicrobial exposure. However, an essential criterion for the study should be careful selection of study herds, if only a small subsample is feasible, as results may be biased, if only farmers already interested in research or with surplus energy submit data.

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Appendix I

Appendix I lists the animal species, age groups and disease groups registered in VetStat. For age groups, standard weights in kilograms are also shown (*in parenthesis*)

Animal species	Age group (standard weight in kg)	Diagnostic group
Pigs	Breeding animals, gilts, suckling pigs (200)	
	Weaners (15)	
	Finishers (50)	Reproduction, urogenital system Udder
Cattle	Bulls, cows (600)	Gastro-intestinal system
	Calves <12 months (100)	Respiratory system
	Heifers, steers (300)	Joints, limbs, hooves, CNS, skin Metabolism, digestion, circulation
Sheep, goats	>12 months (50)	
	<12 months (20)	
Mink	Not recorded (1)	Other (mink only)
Aquaculture	Not recorded (1)	Red mouth disease
		Furunculosis
		Brood syndrome
		Other
Poultry	Broilers (0.2) Layers (1) Rearing flocks (1)	Coccidiosis
		Enteritis
		Hepatitis
		Salpingitis
		Other
		Respiratory system/organs
Other production animals*	Not recorded (1)	
Horses	Not recorded (500)	Not recorded
Pets	Not recorded (<i>not given</i>)	

*llamas, rabbits, deer, ostriches
(Anonymous, 2015b)

Appendix II

Appendix II gives a brief overview of the present research projects of the interinstitutional panel's group members, who contributed to paper I.

Name	Title	Institution	Present projects
Nana Dupont	PhD student	University of Copenhagen - Department of Large Animal Sciences	Description and evaluation of Vetstat data on pig antimicrobial usage
Mette Fertner	PhD student	Technical University of Denmark - National Veterinary Institute	Correlations between health, welfare and antimicrobial use in Danish pig herds
Anna Camilla Birkegård	PhD student	Technical University of Denmark - National Veterinary Institute	Veterinary epidemiology with emphasis on the association between spatial proximity, contact structures, antimicrobial consumption and antimicrobial resistance
Amanda Brinch Kruse	PhD student	University of Copenhagen - Department of Large Animal Sciences	Alternatives to antimicrobial treatment in pigs: effect of vaccines and biosecurity on antimicrobial use
Gitte Blach Nielsen	PhD student	University of Copenhagen - Department of Large Animal Sciences	Economic benefit of control of infectious respiratory diseases in swine with emphasis on the use of vaccines
Vibe Dalhoff Andersen	PhD student	Technical University of Denmark - National Food Institute	Epidemiology of zoonotic antimicrobial resistance in animal production, contributor to DANMAP-reports
Leonardo Victor de Knegt	Assistant Professor	Technical University of Denmark - National Food Institute	Predictive modelling for development of antimicrobial resistance in pig herds, contributor to DANMAP-reports

Appendix III

Information gathered in relation to study 3.

Information gathered	Information source	Information type
Antimicrobial usage (Total kg of active ingredient registered for use in pigs according to age group)	VetStat	Quantitative, continuous
Change in primary veterinarian* (yes/ no)	VetStat	Qualitative, dichotomous
Type of production (organic/ free-range/ conventional; production/ breeding facility)	CHR*	Qualitative, nominal
Number of pigs (In age group with a registered reduction in antimicrobial usage on 31 December 2010)	CHR*	Quantitative, continuous
Closure of herd (yes/ no)	CHR website and the herd's affiliated veterinarian	Qualitative, dichotomous
Change of owner (yes/ no)	CHR website, cross-checked with information from questionnaires	Qualitative, dichotomous
Expansion of buildings or change in number of pigs at stable during the study period (yes/ no)	Telephone interview and questionnaire	Qualitative, dichotomous
Major disease outbreak** (yes/ no)	Telephone interview and VetStat	Qualitative, dichotomous
Specific Pathogen Free-status (conventional/ SPF-herd)	Telephone interview	Qualitative, nominal
Known herd health status (<i>M. hyopneumoniae</i> , <i>A. pleuropneumoniae</i> , toxicogenic <i>P. multocida</i> , <i>S. scabiei</i> var. <i>Suis</i> , <i>T. hyodysenteriae</i> , Porcine Reproductive and Respiratory Syndrome, lice)	Questionnaire	Qualitative, nominal
Eradication program performed (yes/ no)	Telephone interview	Qualitative, dichotomous
Data on mortality and/or daily weight gain (yes/ no)	Telephone interview	Qualitative, dichotomous
Produced finishers sent to Danish Crown slaughter facility (yes/ no)	Telephone interview	Qualitative, dichotomous
Change of slaughter facility (yes/ no)	Telephone interview	Qualitative, dichotomous

Appendix IV

Page 143: Initial questionnaire for phone interview (exclusion criteria)

Page 148: questionnaire sent to farmers

Page 151: questionnaire sent to veterinarians

Date_____

ID _____

CHR number_____

Name of herd owner/herd manager_____

Veterinarian_____

Age groups in the herd_____

1. Do you keep IT-based reports on productivity?

(Please choose only one answer)

a. Yes

b. No

2. Do you have a Health Advisory Agreement?

(Please choose only one answer)

a. Yes

b. No

3. Has the herd changed owner in the period 1 June 2009-31 May 2011?

(Please choose only one answer)

- c. Yes
- d. No

If yes, then please state when _____

4. (If finishers) Do you send finishers from this herd for slaughter in a Danish Crown abattoir?

(Please choose only one answer)

- a. Yes
- b. No

5. (If yes to question 5) Have you sent finishers to different abattoirs in the period 1 June 2009-31 May 2011?

(Please choose only one answer)

- c. Yes
- d. No

6. Does the herd have an SPFhealth status or is it a conventional herd?

(Please choose only one answer)

- a. SPF-blue
- b. SPF-red
- c. SPF-green
- d. Conventional
- e. Free-range
- f. Other (state which)

Please use capital letters

7. Have you in the period 1 June 2009-31 May 2011 had any changes in number of pigs at stable of 10% or more?

(Please choose only one answer)

- a. No
- b. Yes (Please state which age group)

--

Please use capital letters

8. Have you in the period 1 June 2009-31 May 2011 taken any new buildings into use?

(Please choose only one answer)

- c. No
- d. Yes (Please state age group and date)

--

Please use capital letters

9. Have you in the period 1 June 2009-31 May 2011 ceased having one or more age groups in the herd?

(Please choose only one answer)

- a. No
- b. Yes (Please state which age group)

--

Please use capital letters

10. Have you in the period 1 June 2009-31 May 2011 performed any eradication programs?

(Please choose only one answer)

- a. No
- b. Yes (*Please state against what*)

Please use capital letters

11. (If exclusion) may we call again if we change the exclusion criteria?

(Please choose only one answer)

- a. No
- b. Yes
- c.

If included

12. May we send a questionnaire?

(Please choose only one answer)

- a. No
- b. Yes

13. May we have data on mortality and daily weight gain (if finishers also abattoir data)?

(Please choose only one answer)

- a. No
- b. Yes

14. Do you wish a copy of the results?

(Please choose only one answer)

a. No

b. Yes

Email _____

15. Is the address we have correct?

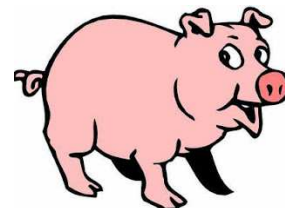
(Please choose only one answer)

a. Yes

b. No (state address)

State the correct address _____

Name herd owner/herd manager



Street (herd)

Town (herd)

Herd identification code (CHR)

General questions

1. Has there been any change in herd owner during the period 1 June 2009 – 31 May 2011?

(Please choose only one answer)

- a. No
- b. Yes (Please state when and name of current owner)

dd-mm-yyyy + name

2. What is the name of the veterinarian who is primarily affiliated to the herd?

Please use capital letters

3. What is the current SPF status of the herd?

(Any number of boxes can be ticked)

- a. Conventional – no SPF-**status**
- b. **Myc**
- c. **Nys**
- d. **Dysenteri**
- e. **DK**
- f. **VAC**
- g. **PRRS**
- h. **Lice**

- i. Sarcoptes
- j. AP2
- k. Ap6
- l. Other AP-types (Please state which)

--	--	--	--

AP-type

4. Has the herd changed SPF status in the period 1 June 2009-31 May 2011?

(Please choose only one answer)

- c. Yes
- d. No

Production

5. Which age groups do you have in this herd (CHR number)?

((Any number of boxes can be ticked))

- a. Sows
- b. Boars
- c. Pre-weaning pigs
- d. Weaners
- e. Finishers
- f. Gilts

Turn →

Medicine

6. What can the herd's decrease in antimicrobial consumption be attributed to according to your opinion?

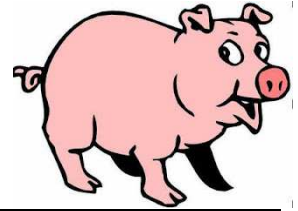
((Any number of boxes can be ticked))

- a. Increased use of vaccines
- b. Smaller dosage of product
- c. Less herd medication
- d. Shorter treatments
- e. Staff education
- f. Change of antimicrobial product
- g. Other (please state what)

Thank you for your aid in the project

Name veterinarian

Veterinary practice, address of veterinary practice



General questions

1. Veterinary identification number _____

2. Veterinary practice number _____

Herds

3. What can the herd's decrease in antimicrobial consumption be attributed to according to your opinion (CHR number xxxxxx, name of herd owner and address of herd)?
((Any number of boxes can be ticked))

- h. Increased use of vaccines
- i. Smaller dosage of product
- j. Less herd medication
- k. Shorter treatments
- l. Staff education
- m. Change of antimicrobial product
- n. Other (please state what)

Thank you for your aid in the project