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Quantify, Explain and Reduce Antimicrobial Usage in Pig Production in Europe

JURY

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Foreword

The work conducted as part of this PhD was carried out in collaboration between SAFOSO AG, a consultancy company located in Bern, Switzerland and the Biology, Epidemiology and Risk Analysis in Animal Health (BioEpAR) Unit of the Nantes Atlantic College of Veterinary Medicine, Food Science and Engineering (Oniris), Nantes, France. Both institutions were involved in the collaborative European research project 'MINAPIG' (Evaluation of strategies for raising pigs with minimal antimicrobial usage), funded under the European programme Emida Era-Net.

The MINAPIG project ran from 2012 to 2015 and included nine institutions from six European countries, namely: SAFOSO AG, Bern, Switzerland (coordinator); Danish Agricultural and Food Council, Copenhagen, Denmark; Oniris, Nantes, France; Universiteit Gent, Ghent, Belgium; University of Veterinary Medicine, Hannover, Germany; National Veterinary Institute, Uppsala, Sweden; Boehringer Animal Health, Ingelheim am Rhein, Germany; ETH Zurich, Institute for Environmental Decisions (IED), Consumer Behavior, Zurich, Switzerland; Swedish University of Agriculture, Uppsala, Sweden.

The overall objective of the MINAPIG project was to identify and assess strategies that promote pig health and thus indirectly lead to a reduced need for antimicrobial use in the pig industry. More specifically, the project aimed i) to assess the efficacy and effectiveness of specific and unspecific technical alternatives to antimicrobial usage in pig production, ii) to identify drivers impacting on choices of farmers and veterinarians between alternative strategies and iii) to transfer obtained knowledge to veterinarians and farmers to promote sustainable pig production.

The project was structured around three main work packages as presented in Figure 1. Fieldwork was organized in two parts. First, a cross-sectional study was conducted among 227 farrow-to-finish pig farms located in Belgium, France, Germany and Sweden, and provided comprehensive data on farm antimicrobial treatment, biosecurity and other management practices. Second, an intervention study was implemented in 70 farrow-to-finish pig farms across countries, most of which had already participated in the cross-sectional study. The intervention study was used as a basis to assess possible alternatives to antimicrobials and perform an economic analysis of the reduction of antimicrobial usage in pig production. Two postal and online surveys also provided input to work package 2.

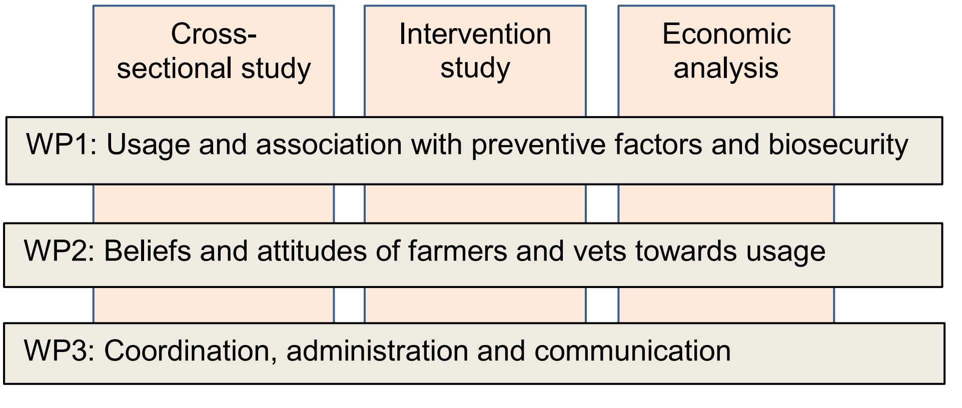

Figure 1. Work plan of MINAPIG research over the 3-year project period

This PhD work was fully part of the MINAPIG project, but was only a piece of this large project. References to other MINAPIG activities are mentioned throughout the text whenever they are needed to facilitate the reading.

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Summary

Antimicrobial resistance (AMR) has become a major threat for public health. The European Centre for Disease Prevention and Control (ECDC) estimated that each year in the European Union, Iceland and Norway, approximately 25,000 patients die from an infection with bacteria resistant to antimicrobials and 4 million patients acquire a healthcare-associated infection (ECDC, 2009). Associated societal costs, including outpatient care costs and productivity losses due to absence from work and premature deaths of infected patients, were estimated to be approximately EUR 1.5 billion each year (ECDC/EMEA, 2009). The global number of human deaths attributable to AMR could exceed the one from other major causes of death e.g. cancer, diabetes or road traffic accidents by 2050, assuming a continued rise in AMR (O'Neill, 2014). Antimicrobial use in food-producing animals contributes to the selection and spread of AMR. Especially pig production contributes to a large part of total antimicrobial use in animals. In order to mitigate the risk arising from antimicrobial use in food-producing animals, a number of international, European and national initiatives have been developed. They aim in particular at promoting the responsible use of antimicrobials and the implementation of alternatives to antimicrobial treatments, reducing total antimicrobial use in food-producing animals by setting reduction targets, and implementing systems to monitor antimicrobial use so that the impact of these strategies can be assessed. However, they face challenges and information gaps, especially related to how to best quantify antimicrobial use, what are the key drivers for antimicrobial use in animals, and what is the feasibility, effectiveness and impact of existing alternatives to antimicrobial treatments.

The objective of this PhD was to address some of these challenges, focusing on the pig sector and working at the herd-level. More specifically, the following research questions were addressed: i) what are the most suitable indicators that should be selected to quantify antimicrobial use, depending on the objectives of a given monitoring system, ii) what is the relative importance of selected technical and psychosocial drivers for antimicrobial usage in pig production, iii) what is the profile of pig farms combining high technical performance and low antimicrobial usage and iv) what is the technical and economic impact of the reduction of antimicrobial usage in pig production. This work was conducted as part of the European project MINAPIG, funded under the programme Emida Era-net, and aiming to identify strategies to improve animal health and reduce the need for antimicrobial use in pig production.

First, a literature review was conducted to develop guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. It was shown that a wide range of indicators is available to quantify antimicrobial usage. The choice of a given indicator strongly influences the interpretation of the results, and can lead to discrepant or even contradictory conclusions. Quantification of antimicrobial usage is currently not harmonized, and few studies justify the choice of the indicator(s) being used. This review showed that for suitable indicators to be selected, the study objective should first be determined. Indeed, depending on whether one wants to monitor antimicrobial usage over time, compare usage between different populations (e.g. different countries) and at different scales (e.g. national vs farm-level), or study the link between antimicrobial usage and AMR, different requirements apply to antimicrobial usage quantification in terms of resolution, comprehensiveness, stability over time, ability to assess exposure and comparability. These requirements were considered to provide recommendations on most suitable indicators for a given study objective. The combination of several indicators applied to the same data was identified as a useful approach to get complementary description of antimicrobial usage.

A cross-sectional study was then conducted to explore, among 227 farrow-to-finish pig farms located in Belgium, France, Germany and Sweden, the main drivers for antimicrobial usage in European pig production. A wide range of drivers were considered, including health status, vaccination scheme, farm performance, farm management, and biosecurity practices as well as farmer's attitudes and perceptions of antimicrobial usage and AMR. The relative importance of these drivers grouped into categories or 'blocks' of drivers was investigated using a statistical method called multiblock partial least squares analysis, recently developed by the French Agency for Food, Environmental and Occupational Health and Safety (Anses). The analysis showed that the contribution of the six selected explanatory blocks was relatively balanced in each country and each block significantly contributed to explaining antimicrobial usage in at least one country. The occurrence of clinical signs, especially respiratory and nervous signs in fatteners, was one of the main drivers in all four countries, whereas the effect of the other blocks of drivers differed between countries. These findings supported the holistic approach which has been promoted so far by national, European and international action plans to tackle the risk associated with AMR (European Commission, 2011; World Health Organization, 2015).

The dataset from the same cross-sectional study was later analyzed from a different perspective. The objective of this second analysis was to explore the profile of so-called 'top-farms' that managed to combine both low antimicrobial use (i.e. treatment incidence below the median use of the country) and high technical performance (i.e. number of weaned per sow per year higher than the national average). A multivariable logistic regression model was developed to explore how the top-farms differed from the 'regular' farms of the study group in terms of herd characteristics, biosecurity and management practices, occurrence of clinical signs and vaccination scheme. Top-farms had fewer gastro-intestinal signs in suckling pigs and fewer respiratory signs in fatteners, which could partly explain their reduced need for antimicrobials and higher performance. They also had higher biosecurity and were located in sparsely populated pig areas. However, a subset of top-farms were located in densely populated pig areas, but still managed to have low usage and high technical performance; they had higher internal biosecurity and more extensive vaccination against respiratory pathogens. These results illustrated that it is possible to control infectious diseases using other approaches than high antimicrobial usage, even in farms with challenging environmental and health conditions.

Subsequently, an intervention study was conducted in order to assess the technical and economic impact of the reduction of antimicrobial usage in pig production. Seventy farrow-to-finish farms located in Belgium, France, Germany and Sweden participated in an intervention study aiming at reducing their antimicrobial use while implementing alternative measures to prevent or control pig diseases at their farm. Herd-specific interventions were defined together with the farmer and the herd veterinarian. Farms were followed up over one year and their antimicrobial usage and technical performance were compared with those from the year before intervention. Compliance with the intervention plan was also monitored. Changes in margin over feed cost and net farm profit were estimated in a subset of 33 Belgian and French farms with sufficient data, using deterministic and stochastic modelling. Results showed that following interventions, a substantial reduction in antimicrobial use was achieved, without impacting the overall farm technical performance. A median reduction of 47.0% of antimicrobial usage was obtained across four countries when expressed in terms of treatment incidence from birth to slaughter, corresponding to a 30.5% median reduction of antimicrobial expenditures. Farm compliance with the intervention plans was high (median: 93%; min-max: 20-100). The median change in the net farm profit among Belgian and French farms was estimated to be €4.46 (Q25-Q75:-32.54; 80.50) and €1.23 (Q25-Q75:-31.12; 74.45) per sow per year using the deterministic and stochastic models, respectively. It was more influenced by the change in the feed conversion ratio and daily weight gain than by the change in antimicrobial expenditures or direct net cost of the intervention. Therefore, costs of alternative measures should not be perceived as a barrier, as long as they contribute to maintain or improve growth performance. The advisory role of the herd veterinarians and other key farm stakeholders should be reinforced to further encourage farmers to engage in the reduction of antimicrobial usage at their farm.

To conclude, this PhD thesis contributed to provide a basis for effective, evidence-based yet affordable strategies to mitigate the risk arising from antimicrobial use in food-producing animals. Several points are still open for discussion. In particular, one may wonder how far the use of antimicrobials in food-producing animals should/could be reduced and what public health benefit can be expected from the reduction of antimicrobial usage in food-producing animals (people being exposed to AMR bacteria via other sources than animals). Additionally, while Europe has strongly engaged in the reduction of antimicrobial usage in food-producing animals, veterinary antimicrobials are being increasingly used in a number of countries worldwide, including for growth promotion. Much more has to be done to further encourage the prudent use of antimicrobials via international collaboration, and to develop solutions at a global scale.

Résumé

La résistance aux antibiotiques est devenue un problème majeur de santé publique. Le Centre européen de prévention et de contrôle des maladies (ECDC) estime que chaque année dans l'Union européenne, en Islande en et Norvège, 25 000 personnes décèdent des suites d'une infection par des bactéries résistantes aux antibiotiques. Les coûts sociétaux associés, qui comprennent non seulement l'augmentation des frais de santé, mais aussi les coûts liés à l'absentéisme et au décès prématuré des patients atteints, ont été estimés à 1.5 milliards d'euros par an. L'utilisation des antibiotiques en élevage contribue à la sélection et la propagation des bactéries résistantes aux antibiotiques. L'élevage porcin en particulier, représente une part importante de la quantité totale d'antibiotiques utilisée en élevage. Reconnaissant l'importance de cette problématique pour la santé publique, de nombreuses initiatives ont été mises en œuvre au niveau international, européen et national, afin de maitriser le risque lié à l'utilisation des antibiotiques chez les animaux d'élevage. Ces initiatives encouragent l'utilisation prudente et raisonnée des antibiotiques, le développement et l'adoption d'alternatives à l'utilisation des antibiotiques, et pour certaines, fixent des objectifs de réduction de l'utilisation des antibiotiques à court et moyen terme. Ces initiatives se heurtent néanmoins à un certain nombre de difficultés, liées notamment à l'absence d'harmonisation des méthodes de quantification de l'utilisation des antibiotiques, à la méconnaissance des principaux déterminants de l'utilisation des antibiotiques en élevage, et au manque de données quant à l'efficacité, la faisabilité et la rentabilité (retour sur investissement) des mesures alternatives aux antibiotiques.

L'objectif de ces travaux de thèse était d'aborder certaines de ces difficultés, en travaillant plus particulièrement à l'échelle de l'élevage porcin, afin d'explorer i) quels sont, pour un objectif donné, les indicateurs les plus adaptés à la quantification de l'utilisation des antibiotiques (Chapitre 2), ii) quelle est l'importance relative des principaux déterminants techniques et psychosociologiques de l'utilisation des antibiotiques en élevage porcin (Chapitre 3), iii) quelles sont les caractéristiques des éleveurs qui combinent à la fois un faible usage en antibiotiques et de bonnes performances techniques (Chapitre 4), iv) quel est l'impact technique et économique de la mise en œuvre de mesures visant à réduire l'usage des antibiotiques en élevage porcin (Chapitre 5). Ces travaux ont été réalisés dans le cadre du projet Européen MINAPIG, financé par le programme Emida Era-net, qui visait à identifier et évaluer des stratégies pour améliorer la santé animale et ainsi réduire le besoin en antibiotiques en élevage porcin.

Suite à une introduction générale (Chapitre 1), le Chapitre 2 propose une étude de synthèse sur le choix des indicateurs de l'utilisation des antibiotiques en médecine humaine et vétérinaire. Il rappelle en premier lieu qu'un très grand nombre d'indicateurs a été proposé en médecine humaine et vétérinaire pour quantifier l'utilisation des antibiotiques. Le choix d'un ou de plusieurs indicateurs est une étape primordiale de toute étude visant à quantifier l'utilisation des antibiotiques, puisqu'il influence significativement l'interprétation des résultats. En effet, plusieurs études ayant appliqué différents indicateurs aux mêmes données d'utilisation des antibiotiques ont conduit à l'obtention de résultats différents, voire contradictoires. Le choix des indicateurs n'est cependant pas harmonisé à ce jour, et peu d'études justifient le choix du ou des indicateurs utilisés. Cette synthèse propose, pour la première fois, de raisonner le choix des indicateurs en fonction de l'objectif de l'étude quantifiant l'utilisation des antibiotiques. En effet, selon que l'on cherche à décrire l'évolution de l'usage des antibiotiques au cours du temps, à comparer les usages entre différentes populations (par exemple différents pays ou différentes espèces) et à différentes échelles (par exemple échelle nationale ou échelle d'un élevage), ou à étudier le lien entre usage et résistance aux antibiotiques, différentes contraintes sont à prendre en compte, en lien notamment avec le niveau de détail requis

(résolution), l'exhaustivité des données, la comparabilité des données au cours du temps et entre différentes populations, ainsi que la capacité de l'indicateur à décrire le niveau d'exposition aux antibiotiques. Le Chapitre 2 propose ainsi, pour chaque objectif, des recommandations quant aux indicateurs permettant de répondre au mieux à ces contraintes, et qui semblent donc les plus adaptés pour quantifier l'utilisation des antibiotiques. Les connaissances actuelles et la diversité des données accessibles ne permettent néanmoins pas d'identifier un unique indicateur comme étant le plus adapté pour un objectif donné. Cette approche n'est d'ailleurs pas forcément nécessaire car l'utilisation de plusieurs indicateurs appliqués aux mêmes données permet de fournir une description complémentaire de l'usage des antibiotiques.

Le Chapitre 3 s'intéresse aux déterminants de l'utilisation des antibiotiques en élevage porcin. Plusieurs études ont montré que l'utilisation des antibiotiques en élevage était non seulement influencée par des déterminants 'techniques', en lien avec la santé des animaux (niveau sanitaire, pratiques de vaccination) et les pratiques d'élevage (conduite, niveau de biosécurité), mais aussi par des déterminants psychosociologiques, liés aux perceptions des éleveurs quant à l'utilisation des antibiotiques, ainsi qu'à leurs habitudes en termes d'utilisation des antibiotiques. L'influence de ces déterminants avait jusqu'à présent été étudiée séparément. L'étude transversale MINAPIG a permis de collecter des données relatives à l'ensemble de ces déterminants au sein d'un même échantillon de 227 éleveurs porcins naisseurs-engraisseurs en Allemagne, Belgique, France et Suède. Dans ce Chapitre, une méthode d'analyse statistique innovante appelée 'méthode de régression multibloc' développée par des chercheurs de l'Anses (Agence française de sécurité sanitaire de l'alimentation, de l'environnement et du travail), a été mise en œuvre afin d'étudier la contribution relative de ces différents déterminants organisés en catégories ou 'blocs' de variables explicatives. L'étude a montré que l'ensemble des six catégories de déterminants considéré dans le modèle contribuait significativement à expliquer l'utilisation des antibiotiques en élevage porcin. La catégorie décrivant la survenue de signes cliniques (signes respiratoires à l'engraissement en particulier) est celle qui contribuait le plus à l'explication des usages d'antibiotiques dans les quatre pays, alors que la contribution des autres catégories de déterminants était plus variable d'un pays à l'autre. Cette étude a permis de conforter l'approche actuelle des plans de maitrise de la résistance aux antibiotiques, qui encourage une approche holistique de la réduction des usages d'antibiotiques en élevage. Si une diversité de déterminants des usages est à prendre compte, il est néamoins essentiel de cibler les mesures proposées via un diagnostic précis des problèmes survenant en élevage.

Dans le Chapitre 4, les données issues de l'étude transversale déjà présentée au Chapitre 3 ont été à nouveau utilisées sous un angle différent ; il s'agissait cette fois d'étudier en détail le profil des éleveurs qui parvenaient à la fois à combiner un faible usage des antibiotiques et un bon niveau de performances techniques. Dans chaque pays, le groupe de ces 'meilleurs éleveurs', dont l'usage était inférieur à l'usage médian des éleveurs du même pays au sein de l'échantillon, et dont le nombre de porcelets sevrés par truie et par an était supérieur à la moyenne nationale, a été comparé, à l'aide d'un modèle de régression logistique, aux autres éleveurs de l'échantillon en termes de conduite et caractéristiques d'élevage, de pratiques de biosécurité, de survenue de signes cliniques et de schémas vaccinaux. L'étude a montré que la survenue de signes gastro-intestinaux chez les porcelets en maternité et de signes respiratoires chez les porcs à l'engraissement était moindre dans le groupe des 'meilleurs éleveurs'. D'autre part, les 'meilleurs éleveurs' avaient un meilleur de niveau de biosécurité et étaient localisés dans des zones de moindre densité porcine (facteur de risque de propagation de maladies infectieuses entre élevages). Néanmoins, un certain nombre d'élevages situés dans des régions de forte densité porcine faisaient partie du groupe des 'meilleurs éleveurs' ; ceux-ci avaient un niveau élevé de biosécurité interne et des pratiques de vaccination renforcées contre les agents pathogènes à visée respiratoire. Ces résultats ont montré qu'il était possible de maitriser les maladies infectieuses (notamment respiratoires) en élevage, en utilisant d'autres méthodes que l'administration d'antibiotiques, même dans des zones de production plutôt à risque d'un point de vue sanitaire, avec une forte densité porcine.

Le Chapitre 5 présente une étude d'intervention visant à évaluer l'impact technique et économique de la réduction de l'usage des antibiotiques en élevage porcin. Ainsi, 70 élevages naisseurs-engraisseurs localisés en Allemagne, Belgique, France et Suède ont participé à une étude d'intervention pour réduire leur utilisation d'antibiotiques, en mettant en œuvre des mesures alternatives de prévention et de contrôle des maladies. Des plans d'intervention spécifiques à chaque élevage ont tout d'abord été définis avec l'éleveur, le vétérinaire et les techniciens en charge du suivi de l'élevage, afin de proposer des mesures adaptées au contexte sanitaire et à la conduite de l'élevage. Le déroulement des interventions a ensuite été suivi au cours d'une année, et les données relatives à l'utilisation des antibiotiques et aux performances de l'élevage ont été comparées à celles observées au cours de l'année avant intervention. Le niveau d'observance du plan et le coût associé à la mise en œuvre de l'intervention ont également été évalués. Les résultats ont montré que suite à la mise en œuvre des interventions, une réduction médiane de 47% de l'utilisation des antibiotiques a été obtenue, exprimée en termes d'incidence de traitement de la naissance à l'abattage, ce qui correspondait à une baisse de 30.5% des dépenses en antibiotiques. Cette réduction a eu lieu globalement sans impact sur les performances des élevages, même si la variabilité observée était relativement élevée. L'observance des mesures était bonne (médiane: 93%; min-max: 20-100). La variation médiane observée du bénéfice net de l'élevage était de €4.46 (Q25-Q75:-32.54; 80.50) et €1.23 (Q25-Q75:-31.12; 74.45) par truie et par an avec les modèles déterministes et stochastiques, respectivement. Cette variation était davantage influencée par la variation du gain moyen quotidien et de l'indice de consommation que par le coût des mesures mises en œuvre. Ainsi, le coût des alternatives aux antibiotiques ne doit pas être perçu comme un frein à la réduction de l'usage des antibiotiques, tant qu'il permet le maintien des performances techniques, en particulier le maintien des performances de croissance. Le rôle de conseiller du vétérinaire et des autres acteurs clés intervenant en élevage doit être renforcé afin d'accompagner davantage d'éleveurs dans une démarche de réduction des usages d'antibiotiques.

Pour conclure, ces travaux ont contribué à la construction d'une base scientifique pour le développement de stratégies efficaces afin de maitriser l'impact de la résistance aux antibiotiques sur la santé publique. Plusieurs problématiques restent encore à résoudre ; on peut se demander notamment jusqu'où peut-on réduire l'utilisation des antibiotiques en élevage et quel bénéfice peut-on espérer de la réduction de l'usage des antibiotiques sur la santé publique (l'homme étant exposé à des bactéries résistantes via d'autres sources que les animaux). Enfin, si l'Europe a fait de gros efforts pour réduire l'utilisation des antibiotiques en élevage, certains pays ont une utilisation en forte augmentation, notamment avec l'utilisation des antibiotiques comme promoteurs de croissance. Une meilleure coopération internationale est donc nécessaire pour encourager la maitrise de la résistance aux antibiotiques au niveau mondial.

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List of Abbreviations

ACD_{kg} : Animal Course Dose

ADD_{kg} : Animal Daily Dose

ALEA : Animal Level of Exposure to Antimicrobials

AMCRA : Center of expertise on Antimicrobial Consumption and Resistance in Animals

AMR : Antimicrobial Resistance

Anses : French Agency for Food, Environmental and Occupational Health & Safety

ATC : Anatomical Therapeutic Chemical classification system

CIA : Critically Important Antimicrobials

DADD or DDDA : Defined animal daily dose

DANMAP : Danish Integrated Antimicrobial Resistance Monitoring and Research Programme

DAPD : DADD per 1,000 animals per day ; estimate of the proportion of animals treated daily with a particular antimicrobial agent

DCD : Number of DDD per 1000 physician contacts per day

DCDvet : Defined Course Dose for Animals

DDD: Defined Daily Dose

DDDvet : Defined Daily Dose for Animals

DID : Number of DDD per 1000 inhabitants per day

DIID : Number of DDD per 1000 insured individuals per day

ECDC: European Centre for Disease Prevention and Control

EFSA: European Food Safety Authority

EMA: European Medicines Agency

ESAC-Net : European Surveillance of Antimicrobial Consumption Network

ESBL : Extended spectrum beta lactamase producing bacteria

ESVAC : European Surveillance of Veterinary Antimicrobial Consumption

EU: European Union

FAO : Food and Agriculture Organization of the United Nations

FCE: Finished Consultant Episode

mpls : Multiblock partial least square analysis

MARAN : Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in The Netherlands

nDDay : Number of DDDvet per animal and per year

NETHMAP : Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands

NORM : Norwegian surveillance programme for antimicrobial resistance in human pathogens

NORM-VET : Norwegian monitoring programme for antimicrobial resistance in the veterinary

and food production sectors

OIE: World Organisation for Animal health

PCD : Number of packages per 1000 physician contacts per day

PCU : Population Correction Unit

PCV-2 : Porcine Circovirus type 2

PID : Number of packages per 1000 inhabitants per day

PIID : Number of packages per 1000 insured individuals per day

PRRS : Porcine Reproductive and Respiratory Syndrome

SPC : summary of product characteristics

SWEDRES : Swedish Antibiotic Utilisation and Resistance in Human Medicine

SVARM : Swedish Veterinary Antibiotic Resistance Monitoring

TCD : Number of treatments per 1000 physician contacts per day

TI200d : Treatment incidence from birth till slaughter

TI_{DDDvet}, TI_{UDDvet} : Treatment incidence based on DDDvet and UDDvet, respectively

TIID : Number of treatments per 1000 insured individuals per day

UDDvet : Used Daily Doses

WHO : World Health Organization

CHAPTER 1: GENERAL INTRODUCTION

1.1 The growing threat of antimicrobial resistance

Antimicrobials are compounds that can kill or inhibit the growth of microorganisms such as bacteria, viruses, fungi or protozoa (Giguère et al., 2013). Since the early days of the antimicrobials era in the 1940's, they have been extensively used and allowed us to achieve extraordinary improvements in human and veterinary medicine. Being an essential tool to prevent and control infectious diseases, they also contributed to the improvement of animal productivity, food security as well as food safety (Rushton et al., 2014). However, the efficacy of antimicrobials has been hampered by the development of resistance mechanisms among bacteria isolates originating from humans, animals, food and the environment (Silbergeld et al., 2008; Finley et al., 2013). Although antimicrobial resistance (AMR) is an old and naturally occurring phenomenon (D'Costa et al., 2011), it is evident that the extensive use of antimicrobials in human and veterinary medicine has strongly accelerated the process of emergence and spread of AMR. Since the discovery of penicillin by Fleming in 1928, every discovery of a new antimicrobial drug was tempered, within few years, by the emergence of bacteria resistant to these drugs (Ohlsen, 2009). Additionally, while many new antibacterial drugs were developed until the 1970s, there is a clear discovery void of new antimicrobial classes since the 1980s, partly due to the fact that pharmaceutical companies have been withdrawing from research in the area (Silver, 2011; World Health Organization, 2014).

Infections with antimicrobial bacteria resistant to antimicrobials lead to treatment failures, more severe or longer infections, as well as deaths. These are especially of concern when resistance develops against critically important antimicrobial agents, i.e. antimicrobial agents which are the sole, or one of limited available therapy to treat serious human diseases, and that are used to treat infections originating from non-human sources (World Health Organization, 2011). A recent example of resistance emergence was the discovery in China of the mcr-1 plasmid-mediated resistance gene coding for resistance to colistin (Liu et al., 2016); colistin is a last resort antimicrobial agent used against Gram-negative bacilli that have developed multidrug resistance such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Paterson and Harris, 2016). It was estimated that each year in the European Union (EU), Iceland and Norway, approximately 25,000 patients died from an infection with bacteria resistant to antimicrobials and 4 million patients acquired a healthcare-associated infection (ECDC/EMEA, 2009). Associated societal costs, including outpatient care costs and productivity losses due to absence from work and premature deaths of infected patients, were estimated to be approximately EUR 1.5 billion each year (ECDC/EMEA, 2009). The global number of human deaths attributable to AMR could exceed the one from other major causes of death e.g. cancer, diabetes or road traffic accidents by 2050, assuming a continued rise in AMR (O'Neill, 2014).

1.2 Relationship between antimicrobial use and resistance

Previous research has shown that the occurrence of AMR is strongly associated with the level of antimicrobial use, both in human (Goossens et al., 2005) and veterinary medicine (Chantziaras et al., 2013). Any antimicrobial use can select for AMR (i.e. not only 'overuse' or 'misuse' which are difficult to define), either directly or via cross- or co-resistance (Lipsitch and Samore, 2002; O'Brien, 2002). Antimicrobial use in humans and animals varies a lot between countries across Europe (Grave et al., 2014; ECDC, 2014), and countries with high levels of antimicrobial use also have higher occurrence of AMR, as demonstrated in the first analysis jointly conducted by the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA), i.e. the institutions in charge of the monitoring of antimicrobial use and AMR in Europe (ECDC/EFSA/EMA, 2015). The latter analysis documented not only an association between antimicrobial use and resistance in food producing animals, but also an association between antimicrobial use in food producing animals and occurrence of AMR in humans for certain combinations of antimicrobial classes/zoonotic bacteria. For example, the probability of clinical resistance to tetracyclins in *Salmonella* Typhimurium, *Campylobacter jejuni* and *Campylobacter coli* isolates from humans was significantly correlated with tetracylins use in food-producing animals in 2011 and 2012. Similarly, the probability of clinical resistance to fluoroquinolons in *Escherichia coli* (*E.coli*) was significantly correlated with fluoroquinolons use in food-producing animals in 2011 and 2012 (ECDC/EFSA/EMA, 2015). However, these results should be interpreted cautiously as the likely source of human resistant infections, e.g. foodborne versus non foodborne source, was unknown. Additionally, antimicrobial use was measured across all food-producing animal species, making it impossible to relate most-likely sources of infection with the animal species where high antimicrobial use occurred.

Still, current evidence strongly suggests that antimicrobial use in animals contributes to the burden of AMR in humans, although the importance and extent of this contribution has yet to be quantified. This hypothesis is further supported by the fact that antimicrobial use in humans and animals rely on the same antimicrobial classes. Possible transmission routes of AMR bacteria or genes include transmission via direct contact with animals, and indirect transmission via animal-derived food consumption, or contact with resistant bacteria released by animals in the environment (Linton, 1977). At this stage, the relative importance of these transmission routes is unknown. Pig farming in particular, has been identified as a potential-source of livestock-associated (LA-MRSA) transmission to pig farmers (Huijsdens et al., 2006) or slaughterhouse personnel (Gilbert et al., 2012), via direct contact with infected animals (ECDC/EFSA/EMEA, 2009). Pigs could also contribute to the foodborne transmission of extended-spectrum-β-lactamase (ESBL) producing bacteria. However, while some countries e.g. the UK reported high prevalence of ESBL producing *E.coli* in animals at slaughter (Randall et al., 2014), the prevalence of ESBL producing *E.coli* in pigs at slaughter seems rather low compared to the prevalence observed in poultry (Madec, 2012). The impact of AMR on pig health seems rather limited to date, and the lack of effective antimicrobials has not yet been reported as a major issue in food-producing animals (Törneke et al., 2015).

1.3 Practices of antimicrobial use in food-producing animals

In food-producing animals, antimicrobials can be used either for growth promotion or for therapeutic purposes. Growth promotion, which consists in administrating antimicrobials via feed to improve animals' feed conversion and therefore reduce the time and total feed needed to grow an animal to market weight (Rushton et al., 2014), is banned in the EU since 2006 (European Commission, 2003). Growth promotion is still allowed in many countries worldwide, including in the United States (US). However, recent US initiatives suggest this could change in the near future. For example, the

‘Guidance for Industry #213’ published in 2013 recommended market authorization holders to remove growth promotion as an indication of treatments with antimicrobial classes that are also used in human medicine, and encouraged those antimicrobials to be delivered under veterinary oversight only. Regarding therapeutic treatments, distinction is usually made between i) preventive treatment, i.e. individual or collective treatment of healthy animals exposed to a risk factor for an infectious disease, ii) metaphylactic treatment, i.e. treatment of clinically sick animals and other animals in the same group that are still clinically healthy but likely to be infected due to close contact with sick animals and iii) curative treatment, i.e. individual or collective treatment only of animals showing symptoms of a disease (Anses, 2014).The EU is currently revising the Directive 90/167/EEC on the manufacturing, placing on the market and use of medicated feed; the revision will likely introduce a ban of the preventive use of medicated feed containing antimicrobials for food-producing animals (European Commission, 2014).

Although antimicrobial use data by animal species are lacking, pig production is recognized as one of the animal production sectors with the highest use of antimicrobials worldwide (Van Boeckel et al., 2015). For example in France in 2014, 36% of veterinary antimicrobials (expressed in tons of active substance) were sold for use in pigs, whereas 23% were sold for use in cattle and 23% for use in poultry (Anses, 2015). In pig medicine, major indications for antimicrobial treatments include digestive disorders in piglets (i.e. neonatal or post-weaning diarrhea) and respiratory disorders in fattening pigs (Chauvin et al., 2002; van Rennings et al., 2015). Antimicrobial treatments are mostly administered via the oral route (i.e. group treatments via feed or water), although some countries e.g. Sweden mostly use parenteral treatments (Sjölund et al., 2016). The relative importance of antimicrobial classes differ from one country to another, but most commonly used classes include penicillins, polypeptids (mostly colistin), macrolides and tetracyclins (Sjölund et al., 2016).

1.4 Strategies to mitigate the risk arising from antimicrobial use in food-producing animals

Recognizing the importance of the growing burden of AMR, and the contribution of antimicrobial use in food-producing animals to this burden, a number of strategies have been developed at international, European and national levels to reduce or contain the risks arising from the use of antimicrobials in veterinary medicine. At international level, the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), the World Health Organization (WHO) collaborating in a Tripartite agreement have identified AMR as one of the three priority topics for joint actions (FAO/OIE/WHO, 2011) and developed a Global Action Plan on AMR (World Health Organization, 2015). The EU also adopted a coordinated and joint strategy to minimize the burden of AMR and in 2011, the European Commission released the Action plan against the rising threats from AMR (European Commission, 2011). National action plans to tackle AMR were further developed by European member states and notably by MINAPIG partner countries Belgium (AMCRA, 2014), France (French Ministry of Agriculture, 2012), Germany (Federal Government of Germany, 2015) and Sweden (Government Offices of Sweden, 2016). All of these strategies point out the need for a holistic and One Health approach, of which the reduction of the overall need for, and use of antimicrobials in food-producing animals is a main goal. Key components of these strategies include the promotion of the responsible use of antimicrobials, the development and implementation of alternative strategies to antimicrobials and the definition of reduction targets. Close monitoring of antimicrobial use is also a key component used to assess the impact of the reduction strategies.

1.4.1 Promotion of the responsible use of antimicrobials

The responsible use of antimicrobials is a key component of the Global Action Plan on AMR (World Health Organization, 2015). The OIE defines the responsible (also called 'prudent') use of antimicrobials as 'a set of practical measures and recommendations intended to prevent and/or reduce the selection of antimicrobial-resistant bacteria in animals' (OIE, 2010). The OIE Terrestrial Animal Health Code on the Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine also clearly defines the responsibilities of relevant stakeholders, i.e. the Competent Authority, veterinary pharmaceutical industry, animal feed manufacturers, veterinarians and food animal producers with regards to the prudent use of antimicrobials (OIE, 2010). These general recommendations are supplemented at European level by more detailed guidelines for prudent use of antimicrobials, such as those developed by the Federation of Veterinarians in Europe (Federation of Veterinarians of Europe, 2012) or the European Platform for the Responsible Use of Medicines in Animals (www.epruma.eu). European member states also developed their own guidelines, for example Denmark (Danish Veterinary and Food Administration, 2013) or Germany (Ungemach et al., 2006), and based on their input, the European Commission also developed Guidelines for the prudent use of antimicrobials in veterinary medicine (European Commission, 2015a). These guidelines aim at promoting antimicrobial stewardship, defined as the optimal selection, dose and duration of an antimicrobial that results in the best clinical outcome for the treatment or prevention of an infection, with minimal impact on subsequent resistance (Gerding, 2001).

A key aspect of the responsible use of antimicrobials relates to the selection of the most appropriate antimicrobial agents. WHO and OIE developed a list of critically important antimicrobials (CIA) for human and veterinary medicine, respectively (World Health Organization, 2011; OIE, 2015); both lists are used as references to help formulate and prioritize risk assessment and risk management strategies for containing AMR caused by human and non-human antimicrobial use. Especially fluoroquinolones, third and fourth generation cephalosporins and macrolides have been categorized as being of highest priority for risk management among those antimicrobials licensed in veterinary medicine (WHO, 2011). The European Medicines Agency also proposed a three-class categorization of antimicrobial substances/classes based on the risk their use in veterinary medicine poses for public health (the risk being low, high, or the substance being not authorized in veterinary medicine) (European Medicines Agency, 2014). High-risk category included those antimicrobial classes listed as CIA by WHO for which the risk to public health from veterinary use was only considered acceptable provided that specific restrictions were placed on their use (i.e. fluoroquinolones and systemically administered third and fourth-generation cephalosporins). These reserve antimicrobials should be used only when there are no alternative antimicrobials authorized for the respective target species and indication (European Medicines Agency, 2014). Following the detection of the mcr-1 resistance gene in China, the European Medicines Agency recommended to add colistin to the high risk category and called for a 65% reduction in colistin sales for veterinary use by 2020, using 2016 as reference year (European Medicines Agency, 2016). Useful insight was also provided by the French Agency for Food, Environmental and Occupational Health & Safety (Anses) that assessed the risks of emergence of AMR associated with modes of antimicrobial use in animals (Anses, 2014). In agreement with the European Medicines Agency categorization, Anses recommended to reserve the use of latest-generation cephalosporins and fluoroquinolones for specific situations, which should be clearly identified by sector and strictly controlled. The French pig sector had already taken action in this direction by introducing in 2010 a volunteer ban on the use of these antimicrobial classes in pig medicine (Anses, 2015). Anses also recommended to abandon preventive practices of antibiotic use, immediately or with a certain delay, to give professionals the time to develop and adopt alternative measures (Anses, 2014).

1.4.2 Development and implementation of alternative strategies to antimicrobials

Most AMR mitigation strategies highlight the importance of reducing the need for antimicrobials by implementing alternative measures; these can be either preventive measures, that will reduce animal bacterial infections in the first place, or control measures using alternative therapies to antimicrobial drugs. The EU Action plan against the rising threats from AMR especially pointed out the importance of preventive measures to reduce antimicrobial use (European Commission, 2011). ‘Prevention is better than cure’ was the motto of the EU Animal Health Strategy 2007-2013 (European Commission, 2007), that formed the basis of the new EU Animal Health Law that entered into force in 2016 (EU Regulation 2016/429). A wide range of preventive measures has been shown, in previous literature, to contribute to reducing the use of antimicrobials in food-producing animals. Examples include reinforced herd biosecurity in order to prevent pathogens from entering into the farm (i.e. external biosecurity) or spreading within the farm once they entered (i.e. internal biosecurity) (Laanen et al., 2013; Postma et al., 2016). Reduced antimicrobial use was also identified as being strongly associated with vaccination, e.g. against Porcine Circovirus type 2 in finishing pig farms (Raith et al., 2016), but vaccinating against more pathogens did not necessarily lead to lower antimicrobial use (Postma et al., 2016). Other promising preventive measures include, among others, improved housing conditions, improved feeding strategies, earlier diagnostic or establishment of infectious disease eradication programmes (Postma et al., 2015).

A wide range of therapeutic alternatives to antimicrobials in the treatment of animal infections are also available. The most popular in pig production is the administration of zinc oxide in feed at 2500 ppm during 14 days after weaning, to control post-weaning diarrhea. Because of the possibility of co-selection for AMR (Baker-Austin et al., 2006) and because of concerns about the release of zinc oxide residues in the environment (Anses, 2013), the therapeutic use of zinc oxide as feed additive in piglets has been controversial in the EU. However, a European market authorization was delivered in 2015, making it available in all EU countries (European Commission, 2015b). Other therapeutic alternatives to antimicrobials include the use of probiotics, prebiotics and ‘competitive exclusion‘ products (i.e. excluding pathogenic bacteria from the host by competition with innocuous bacteria) (Callaway et al., 2008), bacteriophage and phytotherapy, although data are generally lacking about their efficacy, feasibility and return on investment (Joerger, 2003).

1.4.3 Targets to reduce antimicrobial use in food-producing animals

The issue of whether targets for the reduction of antimicrobial use in food producing animals should be specified has been debated. Some consider the reduction of antimicrobial use as an objective in itself, whereas others claim that antimicrobial use in animals should in any case be reduced to a minimum, the ultimate goal being the mitigation of AMR in humans (Törneke et al., 2015). Targets are usually politically motivated rather than evidence-based and therefore set rather arbitrarily, but they have the advantage to provide a basis to monitor reduction achievements. The Review on Antimicrobial Resistance recommended to set a global target to promote a worldwide reduction of veterinary antimicrobial use over the period 2015-2025; it proposed to target an average level of 50 mg of active substance per kg of livestock, which is the level currently used in animals in Denmark, one of the lowest antimicrobial users in the EU (O 'neill, 2015). To date, neither the Global Action Plan on AMR nor the EU Action plan against the rising threats from AMR set antimicrobial reduction targets. These are under the responsibility of national competent authorities of EU member states.

For example, mandatory reduction targets were introduced in the Netherlands in 2009, with the aim to achieve a 20% reduction in total antimicrobial use in animals by 2011 and a 50% reduction by 2013; in 2012, the 50% reduction target was already reached (Mevius and Heederik, 2014). Among MINAPIG participating countries, Belgium and France have set reduction targets. In Belgium, the Center of Expertise on Antimicrobial Consumption and Resistance in Animals (AMCRA, www.amcra.be) announced in the AMCRA 2020 vision statement that Belgium was aiming to achieve, using 2011 as reference year and expressing antimicrobial use in mg of active substance per kg of biomass, a 50% reduction of overall antimicrobial use in animals by 2020, a 75% reduction of the use of quinolones and third and fourth generation cephalosporins by 2020, and a 50% reduction of the use of feed medicated with antimicrobials by 2017 (AMCRA, 2014). France announced in the Plan Ecoantibio 2017 (French Ministry of Agriculture, 2012) it was targeting a 25% reduction of veterinary antimicrobial use between 2013 and 2017. Later, another policy was introduced with the French bill on the Future of Agriculture, Food and Forestry with a target of 25% reduction of the use of quinolones and third and fourth generation cephalosporins between 2014 and 2016 (Anonymous, 2014). To our knowledge, Germany and Sweden have not set explicit, quantitative antimicrobial reduction targets in animals. However, Germany has implemented since 2014 a benchmarking system to compare the frequency of antimicrobial treatments between farms, and farms which antimicrobial use exceeds a given threshold have the obligation to take actions (Federal Government of Germany, 2015). In Sweden, the Swedish Strategy to combat antimicrobial resistance promotes a minimum use of antimicrobials in animals (Government Offices of Sweden, 2016); antimicrobial use in animals in Sweden is indeed among the lowest in Europe (European Medicines Agency, 2015).

1.4.4 Monitoring of antimicrobial use in animals

A key element of strategies to minimize the risks arising from the use of antimicrobials is to be able to monitor antimicrobial use, so that the achieved reduction and changes in antimicrobial use can be assessed. The OIE Terrestrial Animal Health Code has set minimum standards for the monitoring of the quantities and usage patterns of antimicrobial agents in food-producing animals (OIE, 2016). The data collected at minimum should be the weight (in kg) of active ingredient of antimicrobials used in food-producing animals per year. To date, however, a limited number of countries in the world have access to these data (Van Boeckel et al., 2014). Strengthening capacity for the monitoring of antimicrobial use is clearly an objective of the FAO/OIE/WHO Tripartite (World Health Organization, 2015). The WHO Collaborating Centre for Drug Statistics Methodology has developed key material to monitor antimicrobial use in an accurate and reliable manner (www.whocc.no); however, methods for monitoring antimicrobial use are clearly not harmonized today, neither in human nor in animal medicine.

In Europe, veterinary antimicrobial sales data are collected from EU/EEA member states by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project which is run by the European Medicines Agency. An harmonized approach is used and consists in normalizing sales data (expressed as total weight of active substance sold in a year) by the animal biomass at risk of being treated, expressed in terms of PCU (Population Correction Unit, i.e. the estimated total weight at treatment of livestock and slaughtered animals after correcting for import and export) (European Medicines Agency, 2015). The ESVAC monitoring has shown a high variability in antimicrobial sales between European countries, including between MINAPIG participating countries (see Figure 2).

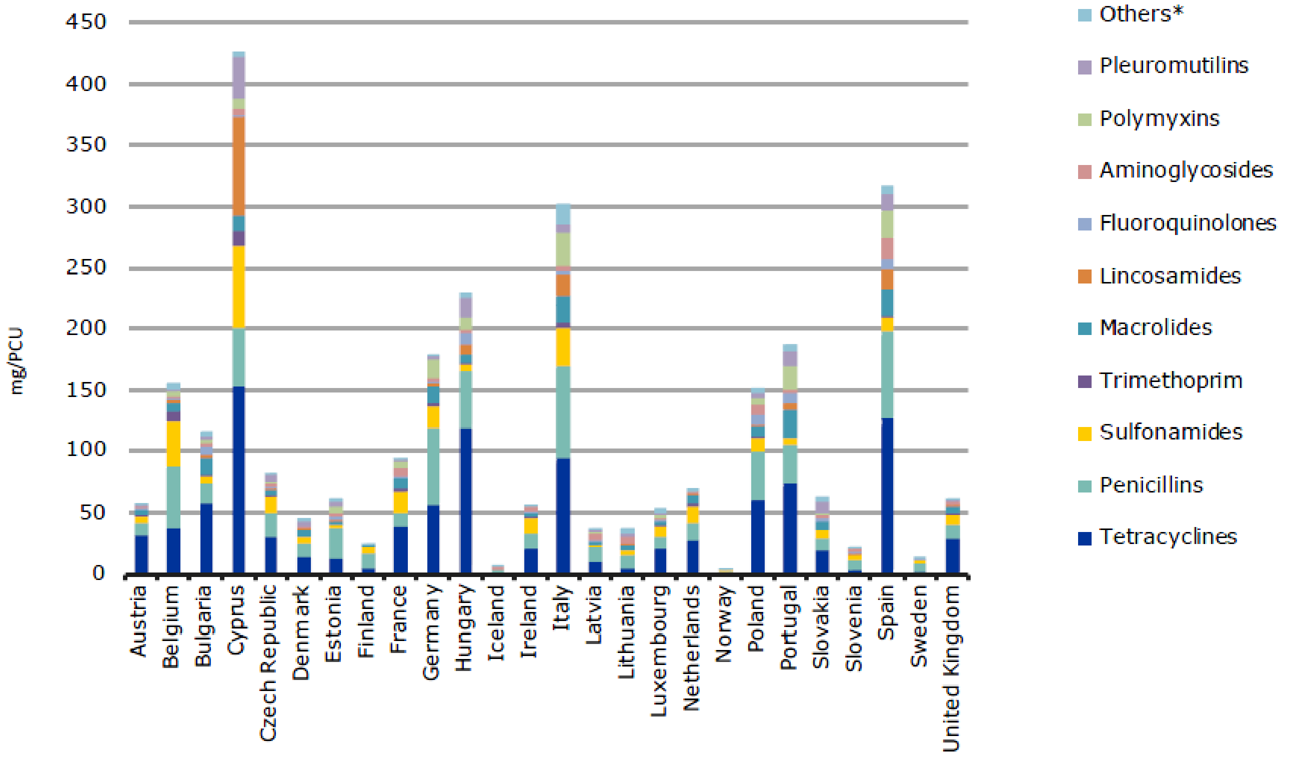

Figure 2. Sales of antimicrobials (in mg active substance/Population Correction Unit) for food-producing animals, including horses, in 26 European countries in 2013. Source: European Medicines Agency, 2015

*Other classes include amphenicols, cephalosporins, other quinolones and other antibacterials

Among the 26 countries included in the ESVAC monitoring in 2013, Germany, Belgium and France had the sixth, seventh and tenth highest sales of antimicrobials for food-producing animals, respectively, whereas Sweden had the third lowest. Between-country comparisons should be made with caution as differences between countries are partly due to differences in animal demographics, in the selection of antimicrobial agents, in dosage regimes and in type of data sources, among other factors (European Medicines Agency, 2015). However, further research conducted within the MINAPIG Consortium using a standardized method confirmed that in farrow-to-finish pig production, Germany had higher usage than Belgium and France, that had higher usage than Sweden, when expressed in terms of treatment incidence from birth till slaughter (TI200), i.e. number of pigs per 1000 receiving a daily dose of antimicrobials from birth till slaughter (Figure 3) (Sjölund et al., 2016).

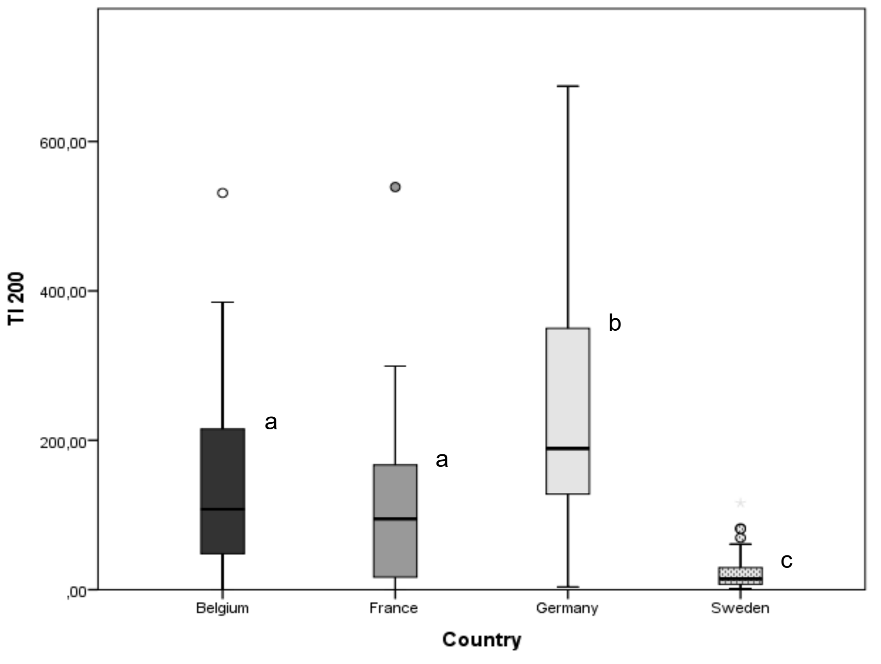

Figure 3. Antimicrobial treatment incidence from birth till slaughter (TI200) in farrow-to-finish pig farms in Belgium (n=47), France(n=60), Germany (n=60) and Sweden (n=60). Source: Sjölund et al., 2016

Different letters denote significant differences in TI200 between countries, using ANOVA testing with Scheffé's method to correct for post hoc comparison.

Country-specific data collected as part of the ESVAC project are also published in national reports, including in Belgium (BelVet-SAC, 2015), France (Anses, 2015), Germany (GERMAP, 2015) and Sweden (Swedres-Svarm, 2015). Other initiatives for the monitoring of antimicrobial use in animals are also conducted at national levels; they include Government monitoring, e.g. the herd-level monitoring system implemented in Germany since 2014 (www.hi-tier.de), as well as private initiatives, e.g. the AB Register system developed by the Belgian accreditation company Belpork (www.registreab.be), the surveys regularly conducted by INAPORC among pig farmers in France (Hémonic et al., 2013), or the Vetproof system developed by the German QS Company (www.vetproof.de). These nationally developed monitoring systems all rely on different methodologies, including different units to quantify antimicrobial use; their results are therefore not comparable.

1.5 Challenges to be addressed by strategies to mitigate the risk arising from antimicrobial use in livestock

For strategies to mitigate the risk arising from antimicrobial use in food-producing animals to be successful, a number of technical, psychosociological and economic challenges should be addressed; the most important of them are described below.

1.5.1 Quantifying antimicrobial use

To be able to assess the impact of strategies to mitigate the risk arising from antimicrobial use in food-producing animals, one should be able to appropriately quantify antimicrobial use, so that variations or differences can be interpreted correctly. This is clearly not the case today. At international level, antimicrobial use data are seriously lacking; a survey conducted by the OIE among 178 OIE Member Countries showed that 73% of them had no official system for collecting quantitative data on antimicrobial use in animals (Diaz, 2013). Data collection in developing countries is especially difficult as over-the-counter selling of antimicrobial drugs is very common (Morgan et al., 2011). In Europe, where quantitative data are generally available, appropriate quantification of antimicrobial use still is an issue. The ESVAC project has been collecting so far data on the total amounts of antimicrobials sold for all food-animal species together (European Medicines Agency, 2015); this is a crude estimate of actual antimicrobial use and does not inform on how, why and by whom antimicrobials were used. Between-country comparison is also seriously challenged by differences in animal demographics, production type and treatment practices, among others (Bondt et al., 2013). Antimicrobial monitoring systems developed by individual countries could provide more accurate information, but they all rely on different methodologies to quantify antimicrobial use. Previous research has shown that the selection of so-called ‘indicators’ of antimicrobial use (i.e. defined as the number of ‘technical’ units of measurement consumed and normalised by the population at risk of being treated in a defined period (European Medicines Agency, 2013)) strongly influences the outcomes of studies aiming, for example, to monitor antimicrobial use trends over time (Coenen et al., 2014) or comparing antimicrobial use between countries (Bondt et al., 2013). It does not mean that a ‘one size fits all’ approach should be used, as antimicrobial use monitoring systems can have different objectives, and therefore, different requirements in terms of how antimicrobial use should be best monitored. However, further work is needed to explore what indicator should be used for a given objective.

1.5.2 Identifying the main drivers for antimicrobial use in livestock

Strategies to mitigate the risk arising from antimicrobial use in food-producing animals aim at promoting the responsible use of antimicrobials and the development and implementation of alternative strategies; this implies key stakeholders, e.g. farmers or veterinarians, to change their current antimicrobial treatment practices. This raises the question of why antimicrobials are used in the first place, or in other words, what are the key drivers for antimicrobial use in food-producing animals. Previous literature has shown that antimicrobial use in pig production is influenced by several types of drivers; these include not only technical drivers, e.g. pig health status (van Rennings et al., 2015), vaccination schemes or biosecurity level (Postma et al., 2016), but also psychosocial drivers that are related, among others, to farmers’ and veterinarians’ attitudes and habits towards antimicrobial usage (Visschers et al., 2015; Coyne et al., 2016). Until now, these drivers have mostly been studied separately, and little is known about the relative importance of a given type of drivers compared to others, and especially about the relative importance of technical versus psychosocial drivers. Additionally, previous qualitative research showed that some pig farms managed to have simultaneously low antimicrobial use and high technical performance (Fertner et al., 2015); it would be interesting to explore how these ‘top farms’ differ from the others in terms of health status, farm management practices and herd characteristics. This should contribute to better inform and target future risk mitigation strategies.

1.5.3 Assessing alternative strategies to antimicrobials

AMR mitigation strategies encourage farmers and veterinarians to implement alternative strategies to antimicrobial treatments, being preventive or control measures. A wide range of alternatives has been proposed in the literature; however, little is known about their feasibility, their effectiveness, i.e. how likely they are to conduct to a substantial reduction of antimicrobial use in a herd, and most importantly how do they impact on the farm technical and associated economic performance. An expert elicitation conducted among 111 European pig health experts identified improved internal biosecurity, external biosecurity and housing conditions as the alternative measures with the highest perceived effectiveness, whereas increased vaccination, increased use of anti-inflammatory products and improved water quality were reported as having the highest feasibility. The highest perceived return-on-investment was reported to be associated with improved internal biosecurity, use of zinc/metals, and increased diagnostics to develop disease control action plans (Postma et al., 2015). Further work is needed to assess whether these findings can be confirmed in the field. Farmers are generally risk adverse (Garforth, 2015), so the question of the feasibility, effectiveness, technical and economic impact of existing alternatives to antimicrobials should first be addressed before we can expect them to be widely implemented at herd level. It is unlikely that a 'golden bullet' alternative that would be feasible, effective and with high return-on-investment in any farm can be identified, but examples of what alternative can be used in which context, to achieve what reduction, and with what impact on the herd performance are needed.

1.6 Scientific objectives of this PhD

The increasing burden of AMR represents a major threat for public health. We now have strong evidence that the burden of AMR in humans is partly related to antimicrobial use in food-producing animals. Pig production especially, contributes to a large part of total antimicrobial use in animals. In order to mitigate the risk arising from antimicrobial use in food-producing animals, a number of international, European and national initiatives have been developed. They aim in particular at promoting the responsible use of antimicrobials and the implementation of alternatives to antimicrobial treatments, reducing total antimicrobial use in food-producing animals by setting reduction targets, and implementing systems to monitor antimicrobial use so that the impact of these strategies can be assessed. However, they face challenges and information gaps, especially related to how to best quantify antimicrobial use, what are the key drivers for antimicrobial use in animals, and what is the feasibility, effectiveness and impact of existing alternatives to antimicrobial treatments.

The objective of this PhD was to address some of these challenges, focusing on the pig sector and working at the herd-level. This should provide a basis for effective, evidence-based yet affordable risk mitigation strategies at higher, i.e. national, European and international levels.

More specifically, the following research questions were addressed:

1. What are the most suitable indicators that should be selected to quantify antimicrobial use, depending on the objectives of a given monitoring system (Chapter 2)?

2. What is the relative importance of selected technical and psychosocial drivers for antimicrobial usage in pig production (Chapter 3)?

3. What is the profile of pig farms combining high technical performance and low antimicrobial usage (Chapter 4)?

4. What is the technical and economic impact of the reduction of antimicrobial usage in pig production (Chapter 5)?

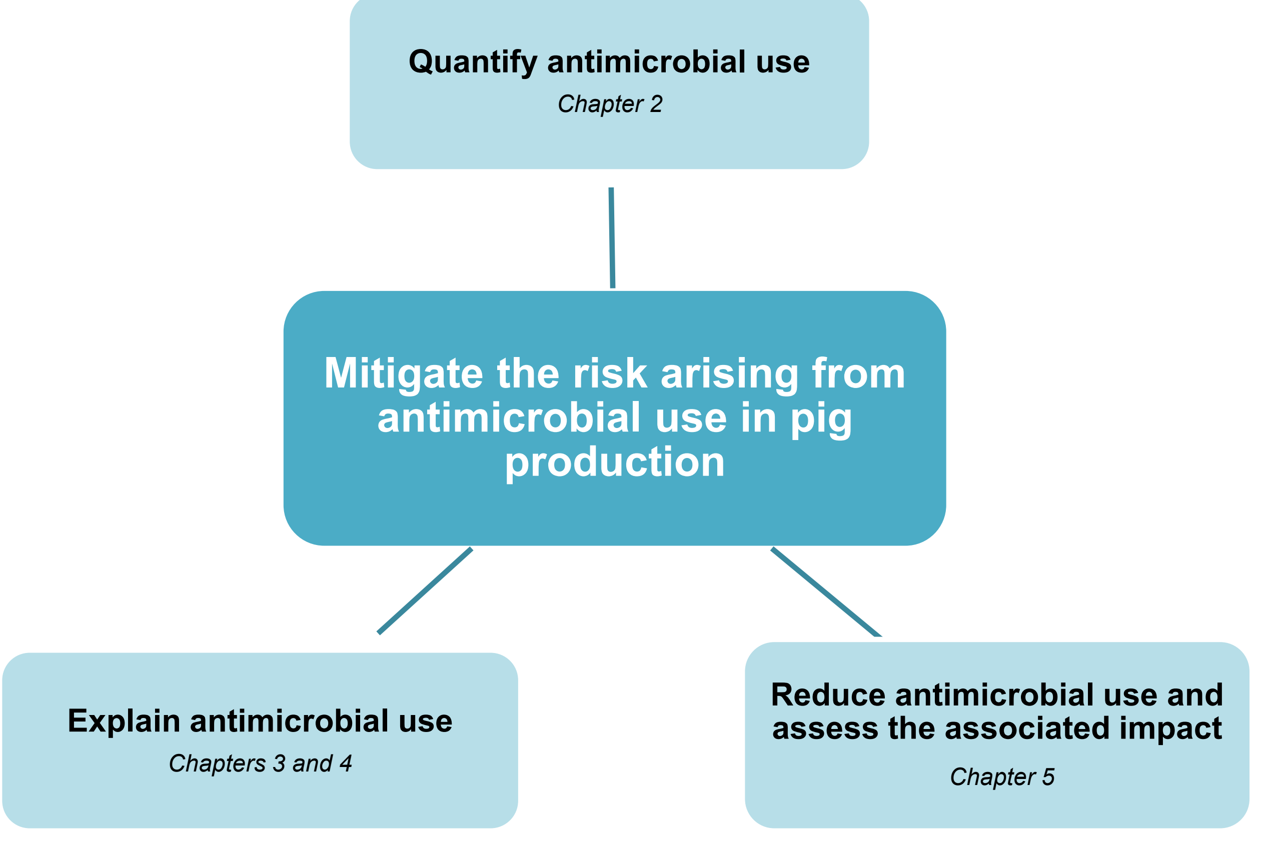

Figure 4. Outlines of the PhD dissertation

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CHAPTER 2: QUANTIFYING ANTIMICROBIAL USE

2.1 Chapter introduction

Any studies exploring antimicrobial use in humans and animals require defining, as a preliminary step, the best approach to quantify antimicrobial use. If the quantification of antimicrobial use in human medicine is relatively harmonized (World Health Organization, 2013), there is still no consensus on how to best quantify antimicrobial use in veterinary medicine. A number of approaches has been developed as part of research activities or as part of the monitoring of antimicrobial use implemented by national competent authorities or private industries. The ESVAC project, working under the umbrella of the European Medicines Agency, is working towards the hamonization of the monitoring of antimiocrobial use in animals in Europe (European Medicines Agency, 2013). However, this work is still in progress.

Previous research has shown that the selection of a given indicator for antimicrobial use strongly influences the outcomes of antimicrobial quantification studies (Chauvin et al., 2001). These include studies aiming at monitoring antimicrobial use over time (e.g. Coenen et al., 2014), comparing antimicrobial use between countries (e.g. Bondt et al., 2011) or between herds (e.g. Chauvin et al., 2008), or exploring the associations between antimicrobial use and resistance (e.g. Schechner et al., 2013).

A preliminary study was conducted as part of this PhD where five indicators of antimicrobial use were applied to the same data collected from 60 French farrow-to-finish herds that participated in the MINAPIG project. The study showed that the selection of a given indicator had a major impact on the identification of the antimicrobial heavy users. This work was presented at the third International Conference on Responsible Use of Antibiotics in Animals, held in Amsterdam, the Netherlands on Sept 29th – Oct1st 2014. Additionally, several indicators were used to explore risk factors for antimicrobial use in pig production (see Chapter 3); depending on the indicators selected, different risk factors for high antimicrobial use were identified (data not shown).

Based on these observations and available literature, it clearly appeared that very cautious selection of antimicrobial use indicators is warranted to be able to correctly interpret antimicrobial quantification studies. However, no recommendations were available regarding what indicators should be used for what study objective. This chapter was a first attempt to fill in this gap.

2.2 Publication

Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals

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2.2.1 Abstract

An increasing variety of indicators of antimicrobial usage has become available in human and veterinary medicine, with no consensus on the most appropriate indicators to be used. The objective of this review is therefore to provide guidance on the selection of indicators, intended for those aiming to quantify antimicrobial usage based on sales, deliveries or reimbursement data.

Depending on the study objective, different requirements apply to antimicrobial usage quantification in terms of resolution, comprehensiveness, stability over time, ability to assess exposure and comparability. If the aim is to monitor antimicrobial usage trends, it is crucial to use a robust quantification system that allows stability over time in terms of required data and provided output; to compare usage between different species or countries, comparability must be ensured between the different populations. If data are used for benchmarking, the system comprehensiveness is particularly crucial, while data collected to study the association between usage and resistance should express the exposure level and duration as a measurement of the exerted selection pressure.

Antimicrobial usage is generally described as the number of technical units consumed normalised by the population at risk of being treated in a defined period. The technical units vary from number of packages to number of individuals treated daily by adding different levels of complexity such as daily dose or weight at treatment. These technical units are then related to a description of the population at risk, based either on biomass or number of individuals. Conventions and assumptions are needed for all of these calculation steps. However, there is a clear lack of standardisation, resulting in poor transparency and comparability. By combining study requirements with available approaches to quantify antimicrobial usage, we provide suggestions on the most appropriate indicators and data sources to be used for a given study objective.

Keywords: antibiotics, technical units, quantification, antimicrobial consumption

2.2.2 Introduction

Antimicrobials have been used widely and successfully for the treatment and prevention of infectious diseases in humans and animals. However, the optimism of the early period of antimicrobial discovery has been tempered by the emergence of bacterial strains resistant to these therapeutics (Levy and Marshall, 2004) that have a serious clinical impact on human (Collignon, 2012) and animal health (Vaarten, 2012). An increasing number of studies have shown that antimicrobial usage in humans (Charbonneau et al., 2006; Costelloe et al., 2010; Sun et al., 2012) and animals (Burow et al., 2013; Hammerum et al., 2014; Simoneit et al., 2015) is the main driver for the development of AMR.

As a consequence, international organisations have encouraged the collection of antimicrobial usage data in order to manage and minimise the further development of AMR (World Health Organization, 2013; World Organisation for Animal Health, 2015a). In this chapter, antimicrobial usage refers to the exposure of a given individual or group over a certain period of time to a certain amount of antimicrobial active substance. The collection of antimicrobial usage data includes both monitoring, i.e. the routine collection of information on antimicrobial usage (Thrusfield, 2013), and punctual data collection from the whole population or from a representative sample of the national population. The data collected can be quantitative only (i.e. amounts of antimicrobials) or include a qualitative description of usage (describing, for example, treatment indication, antimicrobial class, active substance and route of administration). Quantification is based on 'indicators' of antimicrobial usage, defined as the number of 'technical' units of measurement (i.e. the amount of antimicrobials) consumed and normalised by the population at risk of being treated in a defined period (European Medicines Agency, 2013).

An increasing variety of indicators of antimicrobial usage has become available in human and animal medicine but none has been put forward as the most appropriate to measure antimicrobial usage. The main difficulties encountered when trying to identify suitable indicators are related to i) the number of different antimicrobial usage indicators available in both human (Coenen et al., 2014; Fortin et al., 2014) and veterinary medicine (Chauvin et al., 2001), ii) the apparent discrepancies or contradictions between the results obtained from different indicators applied to the same antimicrobial usage data (Chauvin et al., 2001; Polk et al., 2007; Dalton et al., 2007; Chauvin et al., 2008; Bruyndonckx et al., 2014), and iii) the diversity of interests, perceived utility and needs among the stakeholders involved in the collection of antimicrobial usage data (DeVincent and Viola, 2006; Benedict et al., 2012). Indeed, a range of study objectives can be pursued with the collection of antimicrobial usage data. As has been shown for the monitoring of antimicrobial resistance (Lewis, 2002; Hunter and Reeves, 2002) and for disease surveillance in general (Thrusfield, 2013), the study objective should be clearly stated at an early stage of study design in order for a monitoring or surveillance system to be successful. However, most studies do not provide a clear rationale for the selection of a certain indicator and data source to measure antimicrobial usage.

Consequently, the objective of this review is to provide guidance to select the most suitable indicators of antimicrobial usage and data sources in accordance with a specific study objective. Indicators from both veterinary and human medicine are included for two reasons: i) some of the difficulties associated with the quantification of antimicrobial usage are common to both disciplines; each discipline can therefore benefit from the experience gained in the other, and ii) in a One Health context, barriers between the disciplines should be lowered as it becomes critical to develop a common approach to measure antimicrobial usage in humans and animals (ECDC, EFSA and EMA, 2015). The review is structured as follows: first, the principal objectives of measuring antimicrobial usage in humans and animals are described, and, for each objective, the main requirements regarding the way in which antimicrobial usage data should be measured are identified. Next, available indicators of antimicrobial usage in human and veterinary medicine are presented and compared, focusing on those calculated from antimicrobial sales, deliveries and reimbursement data. Finally, suggestions are provided to select the most suitable indicators of antimicrobial usage and data sources in accordance with the study objective.

2.2.3 Why measure antimicrobial usage?

The collection of antimicrobial usage data serves four main objectives. First, antimicrobial usage is measured for the monitoring of antimicrobial usage trends over time (*Objective 1*). A number of countries report annual antimicrobial usage data that are compared to the usage observed in previous years. Reports on antimicrobial usage are communicated either separately for human medicine (Petrov et al., 2005; Mölstad et al., 2008; Meyer et al., 2013; Health Protection Scotland, 2014; Australia Infection Control Service, 2014) and veterinary medicine (Ministry of Agriculture, Forestry and Fisheries of Japan, 2013; Federal Agency for Medicines and Health Products, 2013; Veterinary Medicines Directorate, 2013; Food and Drug Administration, 2014; Anses, 2014) or in a joint report (NORM and NORM-VET, 2012; Public Health Agency of Canada, 2013). European countries also report their antimicrobial usage trends over time in a joint report and using a standardised approach between countries. This work is conducted by the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) for antimicrobial usage in humans (Vander Stichele et al., 2004; Adriaenssens et al., 2011) and by the ESVAC project for veterinary antimicrobial usage (European Medicines Agency, 2014).

Antimicrobial usage monitoring over time makes it possible more specifically to quantify the impact of control strategies or intervention programmes. Examples include the assessment of the effect of the EU ban on antimicrobials as animal growth promotors initiated by Sweden in 1986 (Wierup, 2001; Casewell et al., 2003; Aarestrup et al., 2010) or the assessment of the impact of antimicrobial awareness campaigns (Huttner et al., 2010). While most of the evaluations of intervention programmes aim at quantifying the reduction in the amount of antimicrobials used, some also assess qualitatively the evolution of antimicrobial treatment practices, for example assessing medical doctors' compliance with guidelines on good antimicrobial prescription practices (Ashiru-Oredope et al., 2012). Because the need for antimicrobial treatments is closely related to the disease situation, the monitoring of antimicrobial usage over time can also provide useful information on the temporal evolution of the health situation, for example following the introduction of new vaccines or the emergence of new diseases, e.g. the chronic wasting disease in pigs that emerged in Europe in the 1990s (Jensen et al., 2012).

Antimicrobial usage data also commonly serve to compare antimicrobial usage between different populations, for example different animal species populations (Veterinary Medicines Directorate, 2013; DANMAP, 2013; NETHMAP and MARAN, 2013), human and animal populations (ECDC, EFSA and EMA, 2015) or different countries (Goossens et al., 2007; (Elseviers et al., 2007; Grave et al., 2010) (*Objective 2*). In addition, benchmarking systems were implemented at hospital, outpatient clinic or farm level, with the objective of identifying high antimicrobial users and thus promoting the reduction or more prudent usage of antimicrobials relying on a sort of ‘shame effect’ on heavy users (Jacquet et al., 2011) (*Objective 3*). Such programmes were for example implemented in the USA and Germany to compare antimicrobial usage between the intensive care units of different hospitals (Fridkin et al., 1999; Meyer et al., 2013). Benchmarking between farms has also been routinely implemented nationwide in Denmark (Danish Veterinary and Food Administration, 2011) and in the Netherlands (Bos et al., 2013).

The monitoring of antimicrobial usage also provides useful data to study the association between antimicrobial usage and resistance (*Objective 4*), i.e. to describe how the exposure of humans and animals to antimicrobial treatments relates to the selection of resistant bacteria or genes and to their spread between different epidemiological units (including farms, hospitals or the environment). Several ecological studies conducted at national and European level showed a significant association between national and European aggregated amounts of antimicrobial sales and antimicrobial resistance prevalence (ECDC, EFSA and EMA, 2015), in both human (Goossens et al., 2005; van de Sande-Bruinsma et al., 2008) and veterinary medicine (Chantziaras et al., 2013; Garcia-Migura et al., 2014). Other studies also quantified the association between antimicrobial usage and resistance at farm level (Akwar et al., 2008; Persoons et al., 2011; Agga et al., 2014) or hospital level (Charbonneau et al., 2006). Some studies demonstrated that the development and spread of AMR was related to certain antimicrobial treatment practices, including the choice of a particular administration route (Varga et al., 2009; Burow et al., 2013; Simoneit et al., 2015), use of a specific antimicrobial class, e.g. fluoroquinolone (Taylor et al., 2009), treatment duration (D’Agata et al., 2007) and number of treatment courses (Costelloe et al., 2010).

2.2.4 For each study objective, what are the requirements regarding the measurement of antimicrobial usage?

The study objective entails certain requirements regarding the measurement of antimicrobial usage; these are grouped into five categories: level of resolution, comprehensiveness, stability of the measure over time, ability to assess exposure to antimicrobials, and comparability of the measure between different populations (Table 1).

Table 1. Requirements for the measurement of antimicrobial usage in accordance with the study objective.

		Requirements for the measurement of antimicrobial usage				
Study objective	Expected outcome	Spatial and temporal resolution	Comprehensiveness	Stability over time	Assessment of exposure level and duration	Comparability between populations
1. Monitoring usage trends over time	Antimicrobial usage in a given population over period A in comparison with period B	Low to high	Low	High	Low	Low
2. Comparison of usage between different species or countries	Antimicrobial usage by individual or given biomass of species or country A in comparison with species or country B over a given period of time	Low	Low	Low	Low	High
3. Benchmarking between hospitals, outpatient clinics or farms	Antimicrobial usage by individual or given biomass in hospital/medical or veterinary practice/farm A in comparison with hospital/medical or veterinary practice/farm B over a given period of time	High	High	Low	Medium	High
4. Study the association between antimicrobial usage and AMR	Antimicrobial usage in a population that leads to the selection and spread of AMR over a given period of time	Low (if selection and spread of resistance are considered together) High (if focus on resistance selection)	Low	Low	High	Low

The requirement levels (i.e. low, medium, high) should be read in columns and aim to rank the relative importance of each requirement across the different study objectives.

Spatial and temporal resolution

The level of resolution includes both a spatial and temporal component. The level of spatial resolution relates to where antimicrobial usage is observed; this can be at supra-national level (Wirtz et al., 2010; Adriaenssens et al., 2011; European Medicines Agency, 2014 ; Versporten et al., 2014), national level (Achermann et al., 2011; Bondt et al., 2011; Suda et al., 2014a), farm level (Chauvin et al., 2008; Callens et al., 2012; Pardon et al., 2012; Persoons et al., 2012) or hospital and outpatient clinic level (Arnold et al., 2006; Dumartin et al., 2010). While low spatial resolution is sufficient to compare antimicrobial usage between different species or countries, high resolution is required to compare antimicrobial usage between farms, hospitals or outpatient clinics (i.e. the resolution level should be equal to or higher than the level of the units that are compared). For studies exploring the association between antimicrobial usage and resistance, low resolution level data has been used to quantify the association between antimicrobial usage and level of occurrence of resistant bacteria and strains, which includes both the selection and spread of antimicrobial resistance (van de Sande-Bruinsma et al., 2008; Chantziaras et al., 2013; Garcia-Migura et al., 2014). On the other hand, studies conducted at high resolution level, in particular those relying on time series analysis (Monnet et al., 2004; Aldeyab et al., 2008), can be used to focus on the quantification of the selection of antimicrobial resistance following antimicrobial usage. However, in this type of epidemiological studies, other factors besides antimicrobial usage (e.g. the clonal spread of resistant strains) will always contribute to the observed occurrence of antimicrobial resistance. Spatial resolution of studies monitoring antimicrobial usage trends over time depends on the level of interest and can be low (e.g. using national-aggregated data to monitor national trends) (Wirtz et al., 2010; Grave et al., 2012) to high (e.g. using farm-level data to monitor individual usage) (Aarestrup et al., 2010).

Temporal resolution refers to the frequency with which antimicrobial usage data is collected. Many studies rely on annual antimicrobial usage data, whatever their objectives. However, a limited number of studies collected monthly data to monitor usage trends in outpatient clinics; this made it possible to describe the seasonal variability of usage (Achermann et al., 2011; Suda et al., 2014), or the association between antimicrobial usage and resistance using time series analysis (Monnet et al., 2004). Monthly collection of antimicrobial usage is also routinely implemented in Denmark for human and veterinary antimicrobial products (DANMAP, 2013) and has been used to highlight specific events, such as the effect on antimicrobial usage of the introduction of generic versions of drugs (Chauvin, 2009; Jensen et al., 2010). In animal production, it is sometimes advisable to adapt the temporal resolution to the length of a typical production cycle, e.g. six weeks in broiler production (Persoons et al., 2012) or eight months in veal calf production (Pardon et al., 2012).

One could also consider the specificity of the study’s target population as a third resolution level component. Thus in veterinary medicine, the resolution of antimicrobial usage studies increases from multispecies-aggregated data (European Medicines Agency, 2014), to species-specific data (e.g. pig production) (Obritzhauser et al., 2011), to production type data (e.g. farrow-to-finish pig farms) (Moreno, 2014) and up to age-specific data (e.g. weaner pigs) (DANMAP, 2013). A similar consideration applies to human antimicrobial usage, where national-aggregated data are commonly subdivided into age group or hospital and outpatient usage data (ECDC, 2012), with hospital data possibly further detailed at the hospital unit level (e.g. the intensive care unit or the neonatal and pediatric unit) (Meyer et al., 2003; Grohskopf et al., 2005).

Comprehensiveness of the data collected

The comprehensiveness of antimicrobial usage measurement refers to the capacity to collect usage data from all units in the target population, e.g. from all herds or all hospitals in the country if the study is conducted at farm level or hospital level, respectively. This requirement only applies to benchmarking studies where every single hospital, outpatient clinic or farm is able to compare its own antimicrobial usage with its peers' usage (Meyer et al., 2003; Danish Veterinary and Food Administration, 2011; Bos et al., 2013). For other purposes, a sufficiently large random sample from the population should provide representative data for the whole population. However, in this approach, the sampling is of crucial importance to ensure true representativeness. This type of study often suffers from the need to rely on the willingness of farmers or hospitals to participate and on the availability of the information needed, which may result in some kind of selection bias.

It should be noted that a balance exists between resolution and comprehensiveness. Indeed, although comprehensiveness is quite easily achieved at poor resolution level (e.g. collecting national sales data from a limited number of market authorisation holders), it becomes more resource-demanding to be comprehensive at high spatial (e.g. collecting data from every farm, hospital or outpatient clinic) and temporal (e.g. collecting monthly data) resolution levels. The Danish Vetstat database collecting monthly antimicrobial usage data from all Danish pig farms represents a good example where both high resolution and comprehensiveness were achieved (Jensen et al., 2004). However, the operational costs of such system are substantial; they were estimated to be approximately 200 000 euros on a yearly routine basis for the Vetstat database (Danish Ministry of Food, Agriculture and Fisheries, personal communication, 2015).

Stability over time

Stability means that the measurement of antimicrobial usage is comparable over time; it is mostly relevant for studies aiming to monitor antimicrobial usage trends over time. Stability is challenged by several issues. First, treatment practices, e.g. average weight at treatment and treatment duration tend to change over the years (see for example Chauvin et al. (2008) who described changes in macrolides usage practices in turkey broilers). In addition, the relative importance of antimicrobial active substances and their corresponding administration routes is evolving; this might be because one usage of an active substance has been replaced by another. In France, for example, animal exposure to antimicrobials decreased by 21.7% via the oral route and increased by 8.6% via the parenteral route between 2007 and 2012, mostly due to the reduction in medicated feed usage in livestock (Anses, 2014). Antimicrobial usage was also described as varying seasonally (Ferech et al., 2006; Elseviers et al., 2007), partly following influenza activity (Coenen et al., 2014). In addition, certain characteristics of antimicrobial products themselves are evolving over time. For example, the amount of active substance per package was shown to increase over the years (as the number of units per package and the amount of active substance per unit increased) (Coenen et al., 2014), whereas antimicrobial prices tended to fall following the introduction of generic antimicrobial products (Hoffman et al., 2007). The impact of population demographic changes (including their size and structure, e.g. age group or species distribution) should also be minimised to achieve stability of antimicrobial usage measurement (Kritsotakis and Gikas, 2006).

Assessment of exposure

The extent to which the quantification of antimicrobial usage is able to assess exposure to antimicrobials, which in turn will determine the antimicrobial resistance selection pressure exerted, should also be considered as an important requirement, especially for studies exploring the association between antimicrobial usage and resistance. At this stage it is still not fully determined which of the exposure characteristics (e.g. antimicrobial spectrum of the compound used, frequency of exposure, duration of exposure, level of dose, route of administration) is most influential in terms of the selection pressure exerted. Therefore, there is a clear need for a better understanding of these questions which will subsequently also make it possible to select the most appropriate exposure measurements to incorporate into the quantification systems. The ESVAC project proposed that the description of selection pressure should ideally include both the level of exposure (antimicrobial agent, daily dose administered and numbers of treated individuals) and the exposure duration (European Medicines Agency, 2013).

Comparability between populations

Comparability of antimicrobial usage measurement represents a major challenge and is a critical requirement for studies aiming to compare usage between different populations such as different species, countries, farms, hospitals or outpatient clinics. Indeed, comparability is threatened at the same time by i) the diversity of available antimicrobial treatments (authorised products, dosages, amount of active substance per package, recommended doses) (Postma et al., 2015), ii) the variability of antimicrobial treatment practices between populations (daily dose, weight at treatment, treatment length, mode of administration, prices), iii) the differences in the population at risk of being treated (population size and structure, average weight at treatment), and iv) the choice of the period at risk of being treated (influence of the season or the species' average lifespan). As observed for resolution and comprehensiveness, the combination of measuring detailed exposure and aiming at good comparability is often difficult: in general, the better the information on exposure, the worse the comparability of antimicrobial usage between two populations. As an example, using Danish and Dutch lists of daily doses for pigs gives a correct estimate of exposure in each country, but impairs the comparability of their antimicrobial usage (Taverne et al., 2015). Yet, both requirements can be achieved by working within similar target populations (e.g. species, production types, age groups). This was highlighted by Bondt et al. (2013) who recommended collecting veterinary antimicrobial usage data at least at species level to be able to compare the antimicrobial exposure between different countries using antimicrobial sales data (Bondt et al., 2013).

2.2.5 How is antimicrobial usage measured?

As mentioned above, antimicrobial usage is quantified using indicators defined as the number of 'technical' units of measurement consumed and normalised by the population at risk of being treated in a defined period (European Medicines Agency, 2013). The term 'technical' means that the units of measurement are not used as traditional units of measurement (e.g. kilograms) to measure a physical quantity (e.g. weight) directly, but rather as theoretical reference values to express consumption of antimicrobial agents (European Medicines Agency, 2013).

Direct and indirect access to the technical unit of measurement of antimicrobial usage

The technical units of measurement described in the literature vary substantially; they include the treatment costs, the number of antimicrobial items (i.e. the number of times an antimicrobial appears on prescription) (Scottish Antimicrobial Prescribing Group, 2014) or number of packages used or used daily, the active substance weight, the number of live kilogram-days or individual-days treated (i.e. the product of a given treatment length and a live weight or a number of individuals respectively), the number of individuals or live weight receiving a full treatment course, and the number of individuals treated daily (see Figure 5). Technical units located at the top of Figure 5 are directly accessible; this means that no estimation or approximation is needed to collect them (i.e. exact data are accessible); others require some standardisation and calculation. In addition, some technical units describe the used amount very precisely (e.g. weight of active substance) whereas others are only a remote estimate of the true usage (e.g. medication cost). At national level, information on the numbers of packages sold can be directly collected from manufacturers, wholesalers, pharmacies, prescribing doctors and hospitals or reimbursements (Coenen et al., 2014 ; Bruyndonckx et al., 2014). The corresponding weight of antimicrobial active substance can then easily be deducted by multiplying the number of packages by the package volume and dose (Ministry of Agriculture, Forestry and Fisheries of Japan, 2013; Food and Drug Administration, 2014; European Medicines Agency, 2014). Data directly obtained from manufacturers and wholesalers are exhaustive and relatively easily accessible as they rely on computed data from a limited number of stakeholders. However, it is almost impossible to identify by whom, when and how the antimicrobial products were used. In veterinary medicine in particular, a time delay was observed between sales recorded by manufacturers and their actual usage by farmers (Anses, 2015). In addition, data collected from manufacturers and wholesalers only provide exact amounts of antimicrobials sold for all animal species together. However, many veterinary antimicrobial products are licensed for several species and one needs to allocate the amounts sold to the different species to allow for a normalisation by the relevant population at risk. This can be achieved via several approaches, for example asking the market authorisation holders to provide an estimate of the amount of active substance sold for each species (Anses, 2014), extrapolating from cross-sectional studies at species level (Filippitzi et al., 2014), or simply reattributing the amounts proportionally to the animal species demographics (Bondt et al., 2013). However, in all of these approaches, only an approximation of the distribution will be obtained. The same issue occurs in human medicine when differentiating outpatient from hospital antimicrobial usage data obtained from wholesalers (Vander Stichele et al., 2004).

At high resolution level, antimicrobial treatment costs can be directly recorded from the hospital pharmaceutical expenditures (Arnold et al., 2006; Weese, 2006) or from the farm invoices kept by the farmer and sometimes entered into technical databases (Corrégé et al., 2014). Numbers of packages can also be directly collected at hospital level using pharmacy stock data (Ansari et al., 2003; Schwartz et al., 2007) and at farm level, using for example drug-bottle-collection containers (Dunlop et al., 1998) or farm deliveries (Hémonic et al., 2013). However, collecting *a posteriori* farm delivery data might be tedious in the absence of automated data collection systems. As only individual treatments are prescribed in human medicine, numbers of treated individuals might also directly be collected from the number of insured individuals in countries where insurance systems are in place (Coenen et al., 2014).

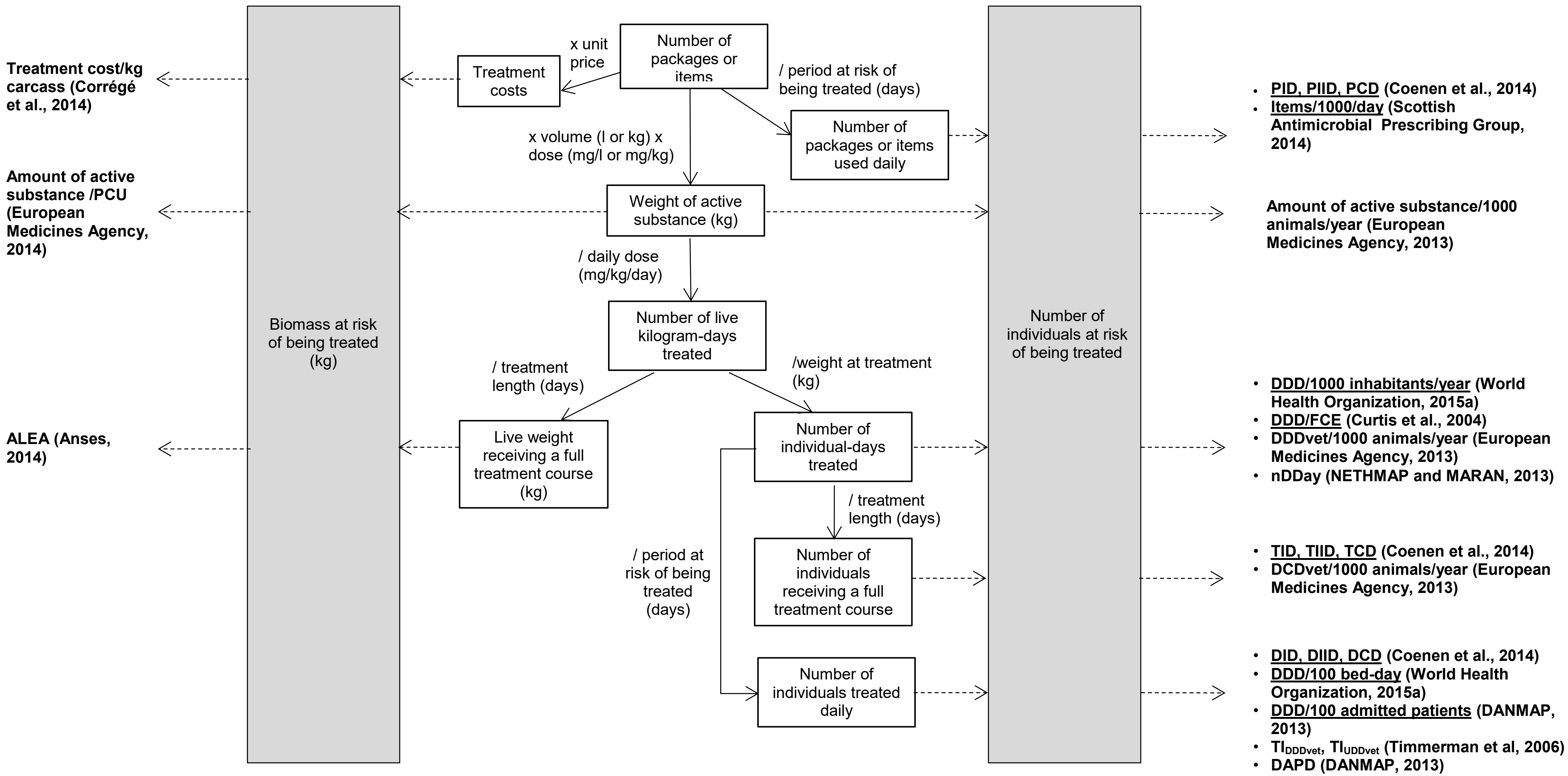

Figure 5. Technical units of measurement indirectly accessed from number of packages or items and corresponding indicators of antimicrobial usage in humans and animals

The white boxes describe the technical units of measurement of antimicrobial usage with the solid arrows representing the calculation steps between them. The grey boxes describe the unit of measurement of the population at risk of being treated. Dashed arrows represent the normalisation of the technical unit of measurement by the population at risk of being treated that leads to the different indicators of antimicrobial usage (in bold). Underlined (respectively non-underlined) indicators are those used in human (respectively veterinary) medicine. DDD= Defined Daily Dose; DDDvet= Defined Daily Dose for Animals; DCDvet= Defined Course Dose for Animals. Please refer to the Appendix S1 for a detailed description of the indicators' calculation formulas. References accompanying the displayed indicators only provide illustrations of possible applications of the indicators and are not intended to be exhaustive.

Figure 5 gives an overview of different technical units of measurement that can be determined from the number of antimicrobial packages or items (and corresponding weight of active substance) in relation to different ways of describing the population at risk of being treated. First, the number of live kilogram-days treated is estimated by dividing the weight of active substance by the daily dose which corresponds to the amount of active substance used per kilogram of individual and per day. The number of individual-days treated is further obtained by dividing the number of live kilogram-days treated by the weight at treatment. Antimicrobial usage can also be expressed as a number of individuals (respectively live weight) receiving a full treatment course, dividing the number of individual-days treated (respectively number of live kilogram-days treated) by the treatment length. A complete treatment course is a course of a given length and dose and the product of the antimicrobial daily dose and the treatment length is commonly called the 'course dose' (Resi et al., 2001; European Medicines Agency, 2013). The number of individuals treated daily is obtained by dividing the number of individual-days by the period at risk of being treated. This period is generally set at one year, but alternative possibilities exist, e.g. using the length of the animal production period (Timmerman et al., 2006).

Measurement unit of the population at risk of being treated

The population at risk of being treated can be considered from two perspectives: i) as a denominator by which antimicrobial amounts are normalised in order to estimate precisely which proportion of the population is exposed to antimicrobials, and ii) as a variable to correct for fluctuations and differences in population demographics and thus to ensure that the measure is repeatable over time and comparable between populations (e.g. countries). The population at risk of being treated is currently expressed using two types of unit: the biomass (or live weight) at risk of being treated and the number of individuals at risk of being treated. The biomass at risk of being treated is usually approximated by the product of the number of individuals at risk of being treated and a standard body weight, the latter being either a standard weight at treatment (ECDC, EFSA and EMA, 2015) or a standard weight of live and slaughtered animals (Anses, 2014). The main advantage of using biomass is that it allows different animal species to be combined within the same population; this is the approach used by the ESVAC project to compute the PCU (European Medicines Agency, 2014). In Denmark, where antimicrobial usage is collected per species and age group, the biomass of a species is calculated by taking into account the average live body-weight and the average life-span of the species (DANMAP, 2013). An important limitation of the biomass concept is the question whether biomass expressed as kg of live weight is a good representation of the actual biomass of concern (microflora) over all species. Therefore it can be concluded that biomass, especially when consisting of a combination of different species, is only a very rough estimate of the population at risk of being treated.

The number of individuals at risk of being treated varies with the study resolution level. In veterinary medicine, this number usually includes both reproductive (also called present or live) and growing (or slaughtered) animals (Anses, 2013; NETHMAP and MARAN, 2013) and can be corrected for export and import of live animals (European Medicines Agency, 2014). Some studies conducted at farm level only focused on growing animals (Timmerman et al., 2006; Pardon et al., 2012). The definition of animal groups (age categories in particular), which can be based on population or herd level data, also influences the number of individuals at risk of being treated. In human medicine, the sources used to inform the number of individuals at risk of being treated are related to the specificity of the target population in which antimicrobial usage is measured. Thus, the number of inhabitants, insured individuals and physician contacts were mostly used to measure outpatient antimicrobial usage (Coenen et al., 2014), whereas the number of occupied beds (World Health Organization, 2015a), number of finished consultant episodes (Curtis et al., 2004) or number of admitted patients (Kuster et al., 2008; DANMAP 2013) were proposed to measure antimicrobial usage at hospital level. However, because the number of occupied beds is more difficult to collect, some studies also use the number of inhabitants to estimate the population at risk of being treated in hospital (Vander Stichele et al., 2004).

Data sources

Figure 5 showed that indirect access to the technical units of measurement of antimicrobial usage requires three parameters to be estimated: the daily dose, the treatment length and the weight of the animal/patient at treatment. Here we present the sources that can be used to inform these parameters.

Data sources to inform daily doses

Daily doses can be presented using standardised international measurement units; in that case, they are conventionally termed “defined” daily doses (i.e. if national or other values are used, the term “defined” is omitted). For human antimicrobial usage, the Defined Daily Dose (DDD) was introduced and defined by WHO as the assumed average maintenance dose per day for a drug used for its main indication in a 70 kg adult (World Health Organization, 2015a). The principle is that a single DDD is attributed by Anatomical Therapeutic Chemical (ATC) code (the latter dividing the antimicrobial active substances into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties) (World Health Organization, 2015a) based on a compromise of the available information including the dose recommended in the summary of product characteristics (SPC) from various countries. The DDD is expressed in milligram per day (the weight at treatment being set at 70 kg), thus the division of the active substance weight by the DDD directly provides a number of individual-days treated (see Figure 5). A similar definition was developed for veterinary products (Jensen et al., 2004) and called Defined Daily Dose for Animals (DDDvet) (European Medicines Agency, 2015) or DADD (DANMAP, 2013) or ADD_{kg} (Anses, 2014) or daily dosages (dd) (NETHMAP and MARAN, 2013); it is expressed in milligram per kilogram and per day. To our knowledge, no international list of DDDvet has been developed so far, but several countries have created their own lists (Anses, 2014; DANMAP, 2013; NETHMAP, 2013). Some discrepancies exist between their respective methodologies; for example, certain countries compute daily doses for animals per licensed product and per animal species (Anses, 2014; NETHMAP 2013), whereas others have developed daily doses for animals listed by active substance, administration route, animal species and age group (DANMAP, 2013). Moreover, where a range of doses is recommended in the SPC, some countries work with median values (Jensen et al., 2004), and others with averages (Postma et al., 2015), maximum values (Anses, 2014) or doses of the main indication (DANMAP, 2013; World Health Organization, 2015a). Another difficulty relates to the definition of daily doses for combined products, with the possibility of counting the combination either as one defined daily dose, regardless of the number of active substances included in the combination (World Health Organization, 2015a), or as the sum of several defined daily doses corresponding to the number of combined active substances (usually two or three). When the sum of defined daily doses is considered, the individual defined daily doses are either the same as those assigned to the single active substance for the same species or a different one (accounting for synergies between combined active substances) (European Medicines Agency, 2015). The ESVAC project is currently developing a common, standardised list of DDDvet across all EU Member States, with priority being given to broiler, cattle and pig antimicrobial products (European Medicines Agency, 2015). A first attempt to develop such a list for pig products was conducted among four European countries (Postma et al., 2015) and clearly showed that huge discrepancies in recommended doses may exist within and between countries for drugs containing the same active substance. This was confirmed by a recent study that highlighted major differences between daily doses for pigs in the Netherlands and in Denmark (Taverne et al., 2015), leading to significant variations in estimates of antimicrobial consumption in pigs in the Netherlands in 2012. Depending on farm types and antimicrobial classes, the usage based on Danish daily doses for animals varied from 55.6% to 171.0% of the usage estimated with Dutch daily doses. Similarly in human medicine, WHO has clearly stated that the DDD is a compromise based on available information about doses used in various countries (World Health Organization, 2015a). This shows that using DDD or DDDvet values implies a generalisation which may sometimes be unwanted. This can partially be avoided through approximating daily doses using the prescribed daily dose or the used daily dose (i.e. the dose actually administered). Different studies in human and veterinary medicine showed that both the prescribed daily doses (Chauvin et al., 2002; Jensen et al., 2004; de With, 2009; European Medicines Agency, 2015) and the used daily doses (UDDvet) (Polk et al., 2007; Callens et al., 2012; Pardon et al., 2012; Persoons et al., 2012; Merle et al., 2014) deviate from the defined daily doses. Where the used daily dose or the prescribed daily dose is lower than the defined daily dose, a calculation based on the defined daily dose will underestimate the number of live kilogram-days treated, the number of individual-days treated, the live weight and the number of individuals receiving a full treatment course as well as the number of individuals treated daily (see Figure 5), and will thus underestimate the antimicrobial usage (Polk et al., 2007; Dalton et al., 2007).

Data sources to inform treatment length

In the same way, treatment length can be estimated from i) the recommended length as defined in the SPC; this source is used to compute the Defined Course Dose for Animals (DCDvet) which is the product of the recommended treatment length and the DDDvet (European Medicines Agency, 2013); the course dose animal is also called ACD_{kg} in France (Anses, 2013), ii) the prescribed treatment length if available, and iii) the administered treatment length as described by the medical doctor, the veterinarian, the farmer or the patient himself/herself (Timmerman et al., 2006; Laanen et al., 2013). Again, recommended treatment lengths were shown to vary substantially between countries, for example for oral antimicrobial products used in pig veterinary medicine (average variation of 7.5 days) (Postma et al., 2015). Administered treatment length may also deviate from prescribed or recommended treatment length (Kardas, 2002; Swinkels et al., 2015). If the actual treatment length is shorter than the recommended one, a calculation based on the recommended treatment length will underestimate antimicrobial usage when expressed as a number of individuals or a live weight receiving a full treatment course.

Data sources to inform weights at treatment

Body weights at treatment are hardly available from field studies although some studies extrapolated them from age at treatment (Chauvin et al., 2005; Timmerman et al., 2006); thus standard weights are usually used. For human antimicrobial usage, body weight is fixed at 70 kg with the exception of a few products used exclusively in children (World Health Organization, 2015a). On the contrary, the average animal body weight at treatment varies substantially between species, production types and age groups. If the actual weight at treatment is lower than the standard body weight (e.g. if antimicrobials are administered to children of 30 kg), a calculation based on the standard weight at treatment will underestimate antimicrobial usage when expressed as a number of individuals-days treated, a number of individuals receiving a full treatment course or a number of individuals treated daily.

The ESVAC project adopted a list of standardised theoretical body weights at the time most likely for treatment for each species in order to compute the PCU (European Medicines Agency, 2014). However, field studies conducted at national level showed that these weights differ significantly between countries, due to different production (e.g. slaughter weights) and treatment practices as well as different definitions of the animal age groups or categories. Thus, different standard weights at treatment are presented in national reports for antimicrobial usage in livestock. For example, veal calves are estimated to be treated on average at 172 kg in the Netherlands (NETHMAP and MARAN, 2013), 86 kg in Denmark (Jensen et al., 2004), 70 kg in France (Anses, 2013) and 140 kg in the ESVAC project (European Medicines Agency, 2014). Standard weights at treatment can also be defined per production type if antimicrobial usage is monitored at this resolution level (DANMAP, 2013).

Indicators of human and veterinary antimicrobial usage

Figure 5 shows the units of measurement for the amount of antimicrobial usage (in the numerator) and the population at risk of being treated (in the denominator) that lead to the calculation of indicators of antimicrobial usage, as well as the relationships between the indicators. For simplicity, this study includes only the indicators presented in English or French scientific articles or national reports and for which the quantification of antimicrobial usage is based on antimicrobial sales, deliveries and reimbursement data. However, these indicators were developed to be used within a particular context and two indicators built on the same technical units of measurement are not necessarily based on the exact same data sources. For example, the indicators called PID and PIID are both calculated from the number of packages used daily normalised by a number of individuals at risk of being treated (Coenen et al., 2014), but for the PID the denominator is the number of inhabitants whereas for the PIID the denominator is the number of insured individuals. Readers are invited to consult the Appendix S1 that provides details of the indicator calculations, highlighting the numerators and the denominators that were used as well as the data sources to inform them.

2.2.6 Comparison of antimicrobial usage indicators

A limited number of studies have compared several indicators applied to the same antimicrobial usage data in order to achieve the same objective. In human medicine, these included some studies analysing the influence of the selection of different indicator numerators (Kern et al., 2005; Muller et al., 2006; Polk et al., 2007; Dalton et al., 2007) and denominators (Curtis et al., 2004; Filius et al., 2005; Kuster et al., 2008) on the comparison and monitoring of antimicrobial usage in hospital settings. For example, Muller et al. (2006) showed that the number of individual-days treated estimated by the DDD approach at a university hospital overestimated the prescribed number of treatment days by 40%. Other studies quantified the discrepancies in the estimation of outpatient antimicrobial usage time trends when working with different numerators and denominators (Coenen et al., 2014; Bruyndonckx et al., 2014). An example is provided by Coenen et al. (2014) who explored outpatient antimicrobial usage in Belgium between 2002 and 2009 and concluded that antimicrobial usage increased when expressed in DDD per 1000 inhabitants per day and decreased when expressed in packages, treatments and insured individuals per 1000 inhabitants per day. In veterinary medicine, some authors applied several indicators based on different numerators to the same data in order to compare antimicrobial usage between countries (Taverne et al., 2015) or farms (Jensen et al., 2004), to monitor usage over time (Chauvin et al., 2008) or to describe discrepancies between used and recommended doses (Persoons et al., 2012). Bondt et al. (2013) investigated the impact of denominator selection when comparing antimicrobial usage based on sales data between countries (Bondt et al., 2013). They showed that antimicrobial usage based on total sales data and expressed in mg of active substance per PCU strongly overestimated the true difference in usage in the Netherlands compared to Denmark, even though the two countries have similar animal demographics.

To further illustrate the differences in outcomes when using different indicators, each indicator presented in Figure 5 was applied to a notional antimicrobial usage dataset in fattening pigs and human medicine. A user-friendly calculation tool was developed in Microsoft Excel to illustrate i) the variability observed in a given indicator calculated from different input data and parameters and ii) the variability observed in a given antimicrobial usage estimate (i.e. with exact same input data and parameters) calculated with different indicators. The tool can be accessed in the supplementary information of Collineau et al. (2016). The observed correlations between indicators varied from 0.34 to 0.97 and were especially weak for indicators based on a number of packages used daily or treatment costs. Explaining difference in outcome between indicators is easier when indicators are directly related (i.e. when numerators are connected by a direct arrow in Figure 5).

2.2.7 Suggestions on technical units, indicators and data sources to be selected in accordance with the study objective

Based on the above described requirements related to the specific study objectives and the available antimicrobial usage measurement approaches, suggestions on preferred technical units and data sources are provided (Table 2).

Table 2. Recommendations for the measurement of antimicrobial usage in accordance with the study objective

	Study objective 1. Monitoring of usage trends over time	2. Comparison of usage between species or countries	3. Benchmarking between hospitals, outpatient clinics or farms	4. Study the association between antimicrobial usage and AMR
Data sources to be used				
Amount of antimicrobials (numerator)	Data collected from national to local level (farm, hospital or outpatient clinic), depending on the resolution level of interest Data can be collected from a population sample	National level data as high resolution is not critical Data can be collected from a population sample as comprehensiveness is not critical	Data at farm, hospital or outpatient clinic as high resolution is critical Census data collection as comprehensiveness is critical	National level data if both selection and spread of antimicrobial resistance are considered Data at farm, hospital or outpatient clinic level if focus on the selection of antimicrobial resistance Data can be collected from a population sample as comprehensiveness is not critical
Parameters	Used or updated standardised daily doses, weights at treatments and treatment duration (based on field studies)	Standardised daily doses, weights at treatments and treatment length	Standardised daily doses, weights at treatments and treatment length	Used daily doses, weights at treatments and treatment length should be used to describe the selection pressure
Population at risk of being treated (denominator)	Correct for changes over time in the size and structure of the population at risk of being treated	Preferably similar and specific target populations (animal species, production types, medical sector) to improve comparability	Preferably similar and specific target populations (animal species, production types, medical sector) to improve comparability	Preferably similar and specific target populations (animal species, production types, medical sector) to relate antimicrobial usage to antimicrobial resistance observed in the corresponding population

Technical unit of antimicrobial usage measurement (numerator)				
Recommended unit	Number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated, number of individuals treated daily, number of packages or items	Number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated, number of individuals treated daily	Number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated, number of individuals treated daily	Number of live kilogram-days treated, the number of individual-days treated and the number of individuals treated daily
Acceptable unit	-[a]	Weight of active substance (if focus on a specific target populations, active substance and administration route)	Treatment costs, weight of active substance, number of items or packages (if focus on a specific target population)	Live weight or number of individuals receiving a full treatment course
Units to be avoided	Treatment costs, weight of active substance (except if short period study where treatment prices and treatment practices are assumed to be constant)	Treatment costs (might be acceptable for comparison between species within the same country), number of items or packages	-[a]	Treatment costs, number of items or packages, weight of active substance
Population at risk of being treated (denominator)				
Recommended unit in human medicine	Number of individuals at risk of being treated	Number of individuals at risk of being treated	Number of individuals at risk of being treated	Number of individuals at risk of being treated
Recommended unit in veterinary medicine	Biomass at risk of being treated (if one or multiple species are included), number of individuals at risk of being treated (if only one species is included)	Biomass at risk of being treated (if one or multiple species are included), number of individuals at risk of being treated (if only one species is included)	Biomass at risk of being treated (if one or multiple species are included), number of individuals at risk of being treated (if only one species is included)	Biomass at risk of being treated (if one or multiple species are included), number of individuals at risk of being treated (if only one species is included)

Period at risk of being treated				
	Annual data to correct for seasonal fluctuations From July to June to capture winter peaks of influenza within the same 12-month period	Fixed time period (e.g. 1 year) or based on length of the animal production period	Fixed time period (e.g. 1 year)	Monthly or quarterly data
Appropriate indicator of antimicrobial usage (corresponding to the above recommended units)				
Recommended indicator in human medicine	In hospital: DDD/FCE, DDD/100 bed-day, DDD/100 admitted patients In outpatient clinics: PID, PIID or PCD (in countries dispensing complete packages), DDD/1000 inhabitants per year, TID, TIID, TCD, DID, DIID, DCD	In hospital: DDD/FCE, DDD/100 bed-day, DDD/100 admitted patients In outpatient clinics: DDD/1000 inhabitants per year, TID, TIID, TCD	In hospital: DDD/FCE, DDD/100 bed-day, DDD/100 admitted patients In outpatient clinics: DDD/1000 inhabitants per year, TID, TIID, TCD, DID, DIID, DCD	In hospital: DDD/FCE, DDD/100 bed-day, DDD/100 admitted patients In outpatient clinics: DDD/1000 inhabitants/year, DID, DIID, DCD
Recommended indicator in veterinary medicine	DDDvet/1000 animals/year, DCDvet/1000 animals/year, nDDay, ALEA, TI_{UDDvet}, DAPD	DDDvet/1000 animals/year, DCDvet/1000 animals/year, nDDay, ALEA, TI_{DDDvet}, DAPD	DDDvet/1000 animals/year, DCDvet/1000 animals/year, nDDay, ALEA, TI_{DDDvet}, DAPD	DDDvet/1000 animals/year, nDDay, TI_{UDDvet}, DAPD
Acceptable indicator in human medicine	-[a]	-[a]	PID, PIID, PCD	TID, TIID, TCD
Acceptable indicator in veterinary medicine	-[a]	Amount of active substance/1000 animals/year, amount of active substance per PCU	Treatment cost/kg carcass, amount of active substance/1000 animals/year, amount of active substance per PCU	DCDvet/1000 animals/year, ALEA

[a] No unit or indicator was considered in this cell

Suggestions to monitor usage trends over time (*Objective 1*)

For studies aiming to monitor antimicrobial usage trends over time, data can be collected from national to local level depending on the relevant spatial resolution level. As comprehensiveness is not critical, data from a representative sample of the population is sufficient. The key requirement is stability over time, so attention should be paid to updating antimicrobial usage parameters: defined daily doses (using the DDD list regularly updated by WHO (World Health Organization, 2015b)), weight at treatment and treatment duration, as well as the size and structure of the population at risk of being treated, as these are dynamic and influential (Kritsotakis and Gikas, 2006; Chauvin et al., 2008). Technical units based on number of daily doses (i.e. number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated or number of individuals daily treated) or packages and items should be preferred, as they correct for possible changes in the relative importance of active substances and corresponding administration routes. Coenen et al. (2014) also recommended using number of packages (instead of DDD based indicators) in countries dispensing complete packages; indeed, number of packages was shown to be a better proxy of antimicrobial prescribing in case the number of units per package (i.e. the pack size) or the dose per unit was increasing over time (Coenen et al., 2014). Treatment costs are better avoided as antimicrobial prices were shown to vary with time; however, treatment costs might be considered for economic or logistical studies over short time periods, where antimicrobial prices and treatment practices are assumed to be constant. The period at risk of being treated is preferably set at one year to correct for seasonal fluctuation in antimicrobial usage patterns (Ferech et al., 2006; Elseviers et al., 2007); July–June years should be preferred in human medicine to capture winter peaks of influenza activity within the same 12-month period (Coenen et al., 2014).

Suggestions to compare usage between species or countries (*Objective 2*)

To compare antimicrobial usage between species or countries, national level data can be used and does not need to be comprehensive. Technical units based on the number of daily doses should be preferred, although the weight of active substance might be acceptable for studies conducted in specific target populations (e.g. same animal species and production type or same hospital department), and focusing on the same active substance and administration route. Parameters should be standardised to be able to compare antimicrobial usage based on the number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated or number of individuals treated daily. As differences in parameters do exist between countries, species, hospitals, outpatient clinics or farms, standardised values need to be defined by consensus (see Postma et al. (2015) for an example). Treatment costs or number of packages and items do not correct for daily dose, weight at treatment and treatment length; thus they should be avoided to compare antimicrobial usage between two populations for any purposes other than economical or logistical ones. Fixed time period or length of the animal production period can be used to define the period at risk of being treated.

Suggestions for benchmarking between hospitals, outpatient clinics or farms (*Objective 3*)

Similar recommendations can be made for the measurement of antimicrobial usage for benchmarking between hospitals, outpatient clinics and farms, although, in that case, census data is required to achieve comprehensiveness. Moreover, antimicrobial usage data should be collected at farm, hospital or outpatient clinic level as high resolution is critical. Number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated or number of individuals daily treated should be preferred to quantify the amount of antimicrobials consumed, although treatment costs, weight of active substance or number of items or packages are acceptable for studies conducted in specific target populations (and when using the weight of active substance, focusing on the same active substance and administration route).

Suggestions to study the association between antimicrobial usage and antimicrobial resistance (*Objective 4*)

To study the association between antimicrobial usage and antimicrobial resistance, data can be collected either at national level, which includes both the selection and spread of antimicrobial resistance (i.e. ecological studies), or at farm, hospital or outpatient clinic level, where the focus is more on the selection of antimicrobial resistance following antimicrobial usage. The number of live kilogram-days treated, the number of individual-days treated and the number of individuals treated daily should be preferred as they take into account the level of exposure and the exposure duration in accordance with the ESVAC project recommendations (European Medicines Agency, 2013). On the contrary, the live weight or the number of individuals receiving a full treatment course does not vary with treatment length; these units rather describe whether or not individuals were exposed, without considering for how long. In addition, the study of the association between antimicrobial usage and resistance should ideally be based on the used daily dose, the actual weight at treatment and the actual treatment length in order to obtain an accurate description of the exposure to antimicrobials. Qualitative data (e.g. administration route, antimicrobial class and spectrum of activity) should also be collected to refine the description of the selection pressure, although at this stage, it is still unclear what exposure characteristics mostly influence the selection pressure exerted. The population at risk of being treated should be selected in accordance with the population under antimicrobial resistance monitoring. In addition, data should be collected at high temporal resolution (e.g. monthly or quarterly data) as the time delay between antimicrobial usage and resistance was shown to be short (i.e. several months) (Monnet et al., 2001).

2.2.8 Conclusion

Several objectives can be pursued by antimicrobial usage studies, implying a number of requirements regarding the way in which antimicrobial usage should be measured. In parallel, a variety of indicators and approaches to measure antimicrobial usage are currently available and result in substantial variation in outcomes and sometimes even apparent discrepancies. By combining study requirements with available approaches to measure antimicrobial usage, we were able to provide some suggestions on the most appropriate indicators and data sources to be used for a given study objective.

At this stage, however, it was not possible to identify a single indicator as being the most suitable for a given objective. This would require a number of data gaps to be addressed, in particular: i) the defining of gold standards for the evaluation of indicators of antimicrobial usage, including for example their sensitivity and specificity, ii) the absence of a scientific basis to identify which parameters better describe antimicrobial selection pressure, and iii) the lack of studies comparing the application of several indicators to the same antimicrobial usage data.

Additionally, in a context of limited resources, it will be difficult to develop multiple monitoring systems that would perfectly suit every individual study objective. To tackle this issue, one could consider i) developing intermediate systems that would imperfectly address a combination of several objectives, ii) promoting the development of parallel monitoring systems (e.g. public-private partnerships) or iii) developing advanced monitoring systems that could properly address several objectives, i.e. using automated data collection at high resolution to compute more accurate indicators; however, these come at a cost.

To conclude, we have shown that some difficulties in measuring antimicrobial usage are common to human and veterinary medicine, and each discipline could certainly benefit from the experience gained in the other to improve its methodology and possibly to develop a common approach that would support the joint analysis of antimicrobial usage data in humans and animals (ECDC, EFSA and EMA, 2015).

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2.3 Conclusion of the chapter

This review was, to our knowledge, the first attempt to develop a structured approach and guidance for selecting indicators of antimicrobial usage in human and animals in accordance with the study objective. Considering selected objectives and associated requirements, as well as available indicators, recommendations were made on the most appropriate indicators for a given study objective. The study also provided a clear view on how available indicators are related to each other, which is often of a confusion to people that are new to the field of antimicrobial quantification studies.

However, major data gaps remain and make it impossible at this stage, to give strict recommendations on the best indicator to be selected for a given objective. These gaps should be addressed in future studies for more specific recommendations to be provided.

This work will certainly contribute to the on-going discussion on the best approach to quantify antimicrobial usage in veterinary medicine. Indeed, the European Medicines Agency recently launched a public consultation on the ESVAC Vision and Strategy 2016-2020 (European Medicines Agency, 2016a) as well as on a concept paper on guidance for the collection of data on antimicrobial consumption by species from national data collection systems (European Medicines Agency, 2016b).

CHAPTER 3: RELATIVE IMPORTANCE OF SELECTED DRIVERS FOR ANTIMICROBIAL USAGE IN PIG PRODUCTION ACROSS FOUR EUROPEAN COUNTRIES

3.1 Chapter introduction

Previous literature has shown that antimicrobial usage in pig production is influenced by several types of drivers, including medical drivers e.g. pig health (Jensen et al., 2012; van Rennings et al., 2015) or vaccination (Postma et al., 2016), and non-medical drivers, e.g. herd characteristics and biosecurity level (van der Fels-Klerx et al., 2011; Postma et al., 2016), as well as farmer's attitudes and habits towards antimicrobial usage (Moreno, 2014; Visschers et al., 2016). However, these drivers have mostly been studied separately; i.e. little is known about the relative importance of a given type of drivers compared to others.

As part of the MINAPIG cross-sectional study, extensive data were collected in a subset of 227 pig farms located in Belgium, France, Germany and Sweden, about potential drivers for antimicrobial usage, including pig health, vaccination scheme, herd characteristics, biosecurity level and farmer's attitudes and habits towards antimicrobial usage. Additionally, the French Agency for Food, Environmental and Occupational Health and Safety (Anses) recently developed and adapted a statistical analysis method called multiblock partial least squares (*mbpls*) analysis, initially used in the fields of chemometrics, sensometrics and process monitoring, to the field of veterinary epidemiology (Bougeard et al. 2011; Bougeard et al., 2011b). The method is especially suitable when a block of several variables has to be explained by a large number of potential risk factors organized in meaningful blocks of explanatory variables. The objective of this study was to explore the relative importance of selected types of drivers for antimicrobial usage in pig production, using this innovative analytic method.

3.2 Publication

Relative importance of selected drivers of antimicrobial usage in pig production across four European countries

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3.2.1 Abstract

Because of the rising threat from antimicrobial resistance, livestock farmers are strongly encouraged to reduce their antimicrobial usage. Previous literature has shown that antimicrobial usage is influenced by a range of drivers, including herd characteristics, biosecurity level, farm performance, occurrence of clinical signs and vaccination scheme, as well as the farmer's attitudes and habits towards antimicrobial usage. However, the effect of these drivers has mostly been investigated separately, and little is known about their relative importance in the explanation of antimicrobial usage.

Using an innovative statistical method called multiblock partial least squares analysis, the objective of this study was to investigate, in a sample of 207 farrow-to-finish pig farms located in Belgium, France, Germany and Sweden, the relative importance of the six above mentioned categories or 'blocks' of drivers for antimicrobial usage in pig production. More specifically, we explored, within each country: i) which blocks of drivers mostly influence overall antimicrobial usage? ii) within each block, which drivers mostly explain antimicrobial usage and iii) do these drivers differ depending on the type of antimicrobial usage (i.e. age group, administration route, antimicrobial class) under study?

Overall, the contribution of the six selected explanatory blocks was relatively balanced in each country and each block significantly contributed to explaining antimicrobial usage in at least one country. The occurrence of clinical signs, especially respiratory and nervous signs in fatteners, was one of the main drivers in all four countries, whereas the effect of the other blocks of drivers differed between countries.

This study provided a basis for the prioritization of future actions to mitigate the risk associated with antimicrobial usage in pig production. Because several categories of drivers were shown to influence antimicrobial usage, a holistic risk mitigation strategy is highly recommended.

Key words: *mbpls* analysis, multiblock analysis, antibiotic

3.2.2 Introduction

Because of the rising threat from antimicrobial resistance, livestock farmers are strongly encouraged to reduce their antimicrobial usage (European Commission, 2011; World Health Organization, 2015). Pig farming in particular contributes to an important part of overall veterinary antimicrobial usage (Van Boeckel et al., 2015). Previous research has demonstrated that antimicrobial usage in food producing animals is influenced by different categories of drivers. First, the herd health status significantly influences the need for antimicrobial treatments, and the observation of clinical signs was reported as the main driver for farmers to initiate an antimicrobial treatment (Friedman et al., 2007); in pig medicine, gastro-intestinal disorders in piglets, respiratory clinical signs in fatteners as well as reproductive clinical signs in sows represent the main indications for antimicrobial therapeutic treatments (Jensen et al., 2012; van Rennings et al., 2015). Antimicrobial usage is also likely influenced by the herd vaccination scheme; herds having reinforced vaccination scheme also appeared to have higher antimicrobial usage, most likely because they used a combination of vaccination and antimicrobial treatments to minimize the impact of infectious diseases at their farm (Postma et al., 2016).

But non-medical drivers are also playing a role. Herd characteristics, such as farm size, production type or management (e.g. farrowing rhythm) were shown to be significantly associated with the amount of antimicrobials used in a herd (van der Fels-Klerx et al., 2011; Fertner et al., 2015; Postma et al., 2016). Farm management practices, especially those related with internal and external biosecurity, also have an impact; the higher the level of biosecurity in a herd, the lower the antimicrobial usage (Chauvin et al., 2005; Arnold et al., 2016; Postma et al., 2016). However, the association between the level of therapeutic antimicrobial usage in a herd and the farm technical performance is not very strong; (Chauvin et al., 2005; van der Fels-Klerx et al., 2011). Recent research has also looked at the influence of farmers' and veterinarians' attitudes and habits towards antimicrobial usage (Moreno, 2014; Coyne et al., 2014); farmers who believed in their ability to reduce antimicrobial usage had higher intention to reduce it (Visschers et al., 2016), and farmers who perceived higher risk of using antimicrobials also had lower actual antimicrobial usage (Visschers et al., 2016). The socio-professional network of the farmer, especially the relationship he/she developed with the herd veterinarian or technical advisor also strongly influences the farmer's practices in terms of antimicrobial treatments (McIntosh and Dean, 2015; Fortané et al., 2015).

In brief, literature has shown that antimicrobial usage in livestock is influenced by a range of drivers, namely the herd characteristics, biosecurity level, occurrence of clinical signs and vaccination scheme as well as the farmer's attitudes and habits towards antimicrobial usage. However, most of the studies cited above only investigated a limited number of those drivers. Therefore, little is known about the relative importance of these different categories of drivers to explain antimicrobial usage, especially the importance of social and psychological, versus technical drivers.

Using a statistical analysis method recently adapted for the veterinary field called multiblock partial least squares (*mbpls*) analysis, the objective of the present study was to investigate, in a subset of 227 farrow-to-finish pig farms located in Belgium, France, Germany and Sweden, the relative importance of different categories of drivers for antimicrobial usage in pig production. More specifically, we explored the following research questions: i) which category(ies) of drivers mostly influences overall antimicrobial usage in each country? ii) within each category of drivers, which factors mostly explain antimicrobial usage and iii) do these factors differ depending on the type of antimicrobial usage (i.e. age group, administration route, antimicrobial class) under study?

This study was conducted as part of the MINAPIG Emida Era-Net project that aims to evaluate strategies for raising pigs with minimal antimicrobial usage.

3.2.3 Material and methods

Study design

A cross-sectional study was conducted in a convenience sample of 227 farrow-to-finish pig farms located in Belgium (n = 47), France (n = 60), Germany (n = 60) and Sweden (n = 60) between December 2012 and January 2014. Farms recruitment was already described in details by Postma et al. (2016); briefly, volunteer Belgian farms were recruited among those subscribing to a newsletter issued by the veterinary faculty of Ghent University and located in the Flanders region (90 % of Belgium pig production (Statistics Belgium, 2013)). French farms were randomly selected from a database of the Institute for pig and pork industry among those located in the north-western part of France (75 % of national pig production (French Institute for pig and pork industry 2013)). German herds were recruited from Niedersachsen, Nordrhein-Westfalen and Mecklenburg-Vorpommern regions (64 % of total German production (Statistisches Bundesamt 2013)) using consultancy circles and input from herd veterinarians. Swedish farmers were invited to participate by their herd veterinarian or a project consortium partner. Inclusion criterion was the presence of more than 70 sows. Each participating farm was visited by one investigator in Belgium, one in France and one in Germany and by two researchers or a veterinarian from the Swedish Animal Health Service in Sweden. A detailed protocol was prepared within the research Consortium and training was organized to harmonize data collection and entry across the four participating countries. Collected data related to antimicrobial usage, herd characteristics and technical performance, biosecurity practices, occurrence of selected signs, vaccination scheme and farmers' attitudes and habits towards antimicrobial usage.

Antimicrobial usage data

Detailed description of antimicrobial usage data collection was provided by Sjölund et al. (2016). Briefly, antimicrobial usage data of the participating farms were collected for one year preceding the farm visit in Belgium, Germany and Sweden and for the last batch in France. In Belgium, invoices from veterinarians and feed companies were combined with information from the farmer. In German farms, dispensing and application forms from the prescribing veterinarian were used. In Sweden, antimicrobial usage data were retrieved from the farmers' treatment records and in France, data were retrieved from the farmers' treatment records together with farmers' directed interview. Collected data included the product commercial name, total volume or mass, concentration of active substance and target animal age category (i.e. sucklers, weaners, fatteners or sows/gilts). In each herd, the average number of animals of each age category present in a batch was estimated using the herd management information system.

Antimicrobial usage was later expressed in terms of 'treatment incidence' (TI) that represents the number of animals per 1000 receiving a daily dose of an antimicrobial on a farm during their production period (Timmerman et al., 2006). The TI was calculated using harmonized Defined Daily Doses Animal (DDDA) as defined by Postma et al. (2015) and harmonized weights at treatment estimated to be 2, 7, 35, 60 and 220 Kg for sucklers, weaners, fatteners, gilts and sows respectively (Sjölund et al., 2016). For each farm were computed separately the TI of each animal age category (i.e. sucklers, weaners, fatteners and sows/gilts), the TI of oral (i.e. via feed, water and per os) and parenteral antimicrobial treatments and the TI of macrolides and cephalosporins/fluoroquinolons treatments; the latter antimicrobial classes were considered to be of special interest as they are considered as critically important for human and veterinary medicine (World Organization for Animal Health, 2015). Topical antimicrobial treatments were excluded from the analysis because these represented a negligible part of total antimicrobial usage (Sjölund et al., 2016).

Herd characteristics and technical performance

Herd characteristics were collected using farmer's interviews and included information on the farm management, i.e. number of present sows, number of employees per 100 sows, farrowing rhythm, weaning age and post-weaning use of zinc oxide, as well as information on the farmer, i.e. age, years of experience with pig farming and highest educational level.

Technical performance data included both growth (i.e. mortality rates in sucklers, weaners and fatteners, daily weight gain and feed conversion ratio in fatteners) and reproductive (i.e. number of litters and weaned pigs per sow and per year) performance and were retrieved from the farm management system when available or via farmer's interviews.

Data on biosecurity practices

Farm biosecurity status was described using the risk-based Biocheck.UGent™ scoring system (http://www.biocheck.ugent.be/); a farm visit together with farmer's interview were used to complete a questionnaire that provided detailed description of farms' practices to prevent pathogens from entering into the farm (i.e. external biosecurity) and to spread within the farm once they entered (i.e. internal biosecurity). Scores between 0 and 100 are then computed for six sub-categories of external and six sub-categories of internal biosecurity practices (Laanen et al., 2013; Postma et al., 2016).

Occurrence of selected clinical signs and vaccination scheme

Farmers were asked to indicate on a scale from 1 (= never) to 5 (= every batch) whether they had to treat their sucklers, weaners, fatteners and sows because of lameness, gastro-intestinal, respiratory or nervous clinical signs, and whether they had to treat their sows because of metritis or mastitis clinical signs. The information was provided for the year preceding the farm visit. Vaccination schemes at the time of the visit were also collected; in particular, farmers had to report whether they were implementing vaccination against porcine parvovirus, *Escherichia coli, Clostridium spp,* atrophic rhinitis, porcine reproductive and respiratory syndrome virus (PRRS), influenza virus, *Mycoplasma hyopneumoniae, Actinobacillus pleuropneumoniae* and porcine circovirus type 2.

Farmers' attitudes and habits towards antimicrobial usage

The collection of data related to farmers' attitudes and habits towards antimicrobial usage was already described in details by Visschers et al. (2015). Briefly, a 7-page paper-and-pencil questionnaire was sent to each farmer beforehand and collected during the farm visit. Questionnaire items mostly relied on 6-point Likert scales (with higher scores corresponding to higher levels of the variables measured) and were a priori grouped, based on their content, into nine constructs exploring the farmer's worries about infectious diseases in his/her pigs, worries about antimicrobial resistance and worries about financial/legal issues, the farmer's perceived benefits of, need for and risks of using antimicrobials in pig production, the farmer's perceptions of the role of the veterinarian and the feed expert regarding the reduction of antimicrobial usage as well as the farmer's perceived impact of selected policy measures to reduce antimicrobial usage (Visschers et al., 2014; Visschers et al., 2015). After checking for high internal reliability of the constructs (i.e. Cronbach alpha >0.6), items scores were grouped together into scale based on the mean of the items scores. Two items related to farmers' habits towards antimicrobial usage ('I only administer antimicrobials to diseased pigs after having consulted my veterinarian' and 'All administrations of drugs are recorded and archived in my farm') had poor internal reliability and were included as individual items in further analysis.

Data analysis

Structure of the multiblock model

Collected data could be organized into seven meaningful blocks of variables, namely: a block of variables to be explained (block **Y**) describing the herd level of antimicrobial usage, and six blocks of explanatory variables, i.e. the potential risk factors, that related with the herd characteristics (block $\mathbf{X_1}$), herd biosecurity practices (block $\mathbf{X_2}$), occurrence of selected signs (block $\mathbf{X_3}$), farm vaccination scheme (block $\mathbf{X_4}$), farmer's attitudes and habits (block $\mathbf{X_5}$) and herd technical performance (block $\mathbf{X_6}$). The six explanatory blocks were made of a total of 59 potential explanatory variables selected from available data on the basis of the main risk factors reported in the literature (Chauvin et al., 2005; van Rennings et al., 2015; Postma et al., 2016; Visschers et al., 2016) and authors' expertise, as well as univariate screening using generalized linear regression analysis applied to each variable of the block **Y**. The composition of the blocks and the distribution of the potential risk factors in each participating country are presented in Table 3. Only three variables were included in the block $\mathbf{X_6}$ because too many data (>20% of the farms) were missing for the other variables of interest (i.e. mortality rates in weaners and fatteners, feed conversion ratio and daily weight gain in fatteners).

Table 3. Definition and description of the variables included in the multiblock model

Definition of variables	% or median (Q25-Q75)			
	Belgium (n=38 herds)	France (n=56 herds)	Germany (n=54 herds)	Sweden (n=59 herds)
Y block : Farm antimicrobial usage				
Log transformed treatment incidence in sucklers	2.11 (1.73-2.36)	1.18 (0.65-1.87)	2.14 (1.88-2.59)	1.73 (1.35-2.06)
Log transformed treatment incidence in weaners	2.42 (1.83-2.86)	2.51 (1.83-2.83)	2.69 (2.45-3.02)	0.85 (0.49-1.28)
Log transformed treatment incidence in fatteners	1.26 (0.23-1.67)	0.00 (0.00-0.11)	1.29 (0.41-1.75)	0.58 (0.43-0.86)
Log transformed treatment incidence in sows/ gilts	0.83 (0.39-1.27)	0.20 (0.10-0.87)	1.03 (0.66-1.57)	0.98 (0.75-1.22)
Log transformed treatment incidence via oral route	2.51 (1.91-2.85)	2.57 (1.89-2.84)	2.73 (2.53-3.03)	0.52 (0.00-1.12)
Log transformed treatment incidence via parenteral route	2.17 (1.86-2.40)	1.30 (0.86-1.89)	2.29 (2.02-2.61)	1.88 (1.52-2.15)
Log transformed treatment incidence with cephalosporins/fluoroquinolons	1.50 (0.79-2.10)	0.10 (0.00-0.62)	1.11 (0.73-1.43)	0.00 (0.00-0.24)
Log transformed treatment incidence with macrolides	1.50 (0.68-2.23)	0.05 (0.00-1.97)	2.06 (0.73-2.45)	0.23 (0.00-0.93)
X_1 block : Herd characteristics				
Number of present sows	287 (211-388)	174 (120-236)	300 (230-495)	190(138-275)
Number of employees per 100 present sows	0.7 (0.5-0.8)	1.05 (0.9-1.3)	0.9 (0.6-1.1)	1.6 (1.2-2.2)
Farrowing rhythm				
1- to 2-week system (%)	23.7	14.3	46.3	13.6
3-week system (%)	26.3	53.6	42.6	18.6
4- to 8-week system (%)	50	32.1	11.1	67.8
Piglets weaning age (days)	24.0 (21.0-25.0)	28.0 (21.0-28.0)	24.0 (21.0-27.0)	35.0 (33.0-35.0)
Farm using ZnO post-weaning (%)	10.5	1.8	7.4	42.4
Age of the farmer (years)	45.5 (33.0-49.0)	44.5 (41.0-52.3)	44.5 (36.5-50.8)	47.0 (43.0-55.5)
Experience with pig farming (years)	23.0 (17.0-26.0)	23.0 (20.0-29.3)	25.0 (16.0-34.3)	22.0 (15.0-30.0)
Highest education level of farm personnel (1=basic to 5=advanced)	3 (3-4)	4 (3-4)	4 (3-5)	3 (3-5)
X_2 block : Herd biosecurity practices[a]				
Purchasing policy	88.0 (84.0-99.0)	70.0 (64.0-78.0)	90.0 (84.5-95.5)	100.0 (84.0-100.0)
Transport, elimination of manure and carcasses	63.0 (57.5-70.0)	61.0 (52.0-70.0)	78.0 (74.5-87.0)	54.0 (40.0-65.0)
Water and feed supply	31.5 (19.5-43.0)	27.0 (27.0-40.8)	47.0 (30.8-47.0)	40.0 (30.0-50.0)
Policy regarding farm visitors	65.0 (53.0-71.0)	59.0 (53.0-71.0)	71.0 (65.0-82.0)	65.0 (47.0-85.0)
Birds, vermin control	55.0 (50.0-70.0)	60.0 (50.0-80.0)	70.0 (60.0-90.0)	80.0 (70.0-90.0)

Definition of variables	% or median (Q25-Q75)			
	Belgium (n=38 herds)	France (n=56 herds)	Germany (n=54 herds)	Sweden (n=59 herds)
Farm location	60.0 (30.0-80.0)	55.0 (27.5-70.0)	30.0 (10.0-57.5)	90.0 (70.0-95.0)
Infectious diseases management	60.0 (40.0-60.0)	40.0 (40.0-60.0)	60.0 (40.0-80.0)	80.0 (40.0-100.0)
Management of the maternity unit	50.0 (36.0-57.0)	57.0 (43.0-65.8)	50.0 (36.0-71.0)	57.0 (43.0-71.0)
Management of the nursery unit	57.0 (43.0-71.0)	71.0 (55.3-74.8)	71.0 (64.0-86.0)	86.0 (71.0-86.0)
Management of the fattening unit	79.0 (57.0-79.0)	79.0 (62.3-79.0)	79.0 (58.8-93.0)	86.0 (79.0-93.0)
Farm compartmentation	39.0 (29.0-50.0)	50.0 (42.0-71.0)	39.0 (32.0-50.0)	43.0 (32.0-54.0)
Cleaning and disinfection	44.0 (29.8-63.0)	45.0 (35.0-65.0)	45.0 (30.0-55.0)	55.0 (35.0-55.0)
X_3 block : Occurrence of clinical signs[b]				
Occurrence of lameness in sucklers	3.0 (2.0-3.8)	3.0 (2.0-5.0)	3.0 (2.0-3.0)	3.0 (2.0-3.0)
Occurrence of gastro-intestinal in sucklers	2.0 (2.0-3.0)	3.0 (2.0-4.0)	2.5 (2.0-3.0)	2.0 (2.0-3.0)
Occurrence of respiratory signs in sucklers	1.0 (1.0-1.8)	1.0 (1.0-1.0)	2.0 (1.0-2.0)	1.0 (1.0-2.0)
Occurrence of lameness in weaners	3.0 (2.0-3.0)	2.0 (1.0-3.0)	3.0 (2.0-3.0)	2.0 (2.0-2.0)
Occurrence of gastro-intestinal in weaners	3.0 (1.3-3.0)	2.5 (1.0-4.0)	3.0 (2.0-4.0)	2.0 (2.0-3.0)
Occurrence of respiratory signs in weaners	2.0 (1.0-2.0)	2.0 (1.0-2.3)	3.0 (2.0-3.0)	2.0 (1.0-2.0)
Occurrence of nervous signs in weaners	3.0 (2.0-3.0)	2.0 (1.0-2.0)	3.0 (2.0-3.0)	2.0 (1.0-2.0)
Occurrence of lameness in fatteners	2.0 (2.0-3.0)	2.0 (1.0-3.0)	2.0 (2.0-3.0)	2.0 (2.0-2.0)
Occurrence of gastro-intestinal in fatteners	1.0 (1.0-1.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Occurrence of respiratory signs in fatteners	2.0 (2.0-3.0)	2.0 (1.0-3.0)	2.0 (2.0-3.0)	2.0 (1.0-2.0)
Occurrence of nervous signs in fatteners	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.8 (1.0-2.0)	2.0 (1.0-2.0)
Occurrence of lameness in sows	3.0 (2.0-3.0)	2.0 (2.0-3.0)	2.5 (2.0-3.0)	2.0 (2.0-2.0)
Occurrence of respiratory signs in sows	1.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (2.0-2.0)	1.0 (1.0-2.0)
Occurrence of metritis in sows	2.0 (2.0-3.0)	2.0 (1.0-2.3)	2.0 (2.0-3.0)	2.0 (1.0-2.0)
Occurrence of mastitis in sows	2.5 (2.0-3.0)	2.0 (1.0-2.0)	3.0 (2.0-3.0)	3.0 (2.0-3.0)
X_4 block : Vaccination scheme				
Vaccination against porcine parvovirus (%)	73.7	98.2	100.0	83.1
Vaccination against *Escherichia coli* (%)	73.7	69.6	44.4	83.1

Definition of variables	% or median (Q25-Q75)			
	Belgium (n=38 herds)	France (n=56 herds)	Germany (n=54 herds)	Sweden (n=59 herds)
Vaccination against *Clostridium spp* (%)	2.6	50.0	27.8	3.4
Vaccination against atrophic rhinitis (%)	55.3	73.2	3.7	1.7
Vaccination against porcine reproductive and respiratory syndrome virus (%)	81.6	64.3	87.0	0.0
Vaccination against influenza virus (%)	18.4	42.9	85.2	0.0
Vaccination against *Mycoplasma hyopneumoniae*(%)	84.2	96.4	88.9	47.5
Vaccination against *Actinobacillus pleuropneumoniae* (%)	10.5	5.4	35.2	1.7
Vaccination against porcine circovirus type 2 (%)	34.2	66.1	94.4	83.1
***X_5* block : Farmer's attitudes and habits**				
Worries about infectious diseases in his/her pigs [c]	4.3 (3.0-5.0)	5.5 (3.9-6.0)	3.5 (3.0-5.0)	3.0 (2.0-4.0)
Worries about antimicrobial resistance [c]	4.2 (3.7-5.0)	5.0 (3.6-5.7)	3.0 (2.3-4.3)	4.0 (3.2-4.7)
Worries about financial/legal issues [c]	5.3 (4.7-6.0)	5.7 (4.9-6.0)	4.3 (3.7-4.7)	4.7 (4.0-5.2)
Perceived benefits of antimicrobial usage in pig production [c]	4.3 (3.7-4.8)	4.0 (3.4-4.5)	4.0 (3.4-4.4)	4.4 (3.6-5.2)
Perceived need for antimicrobial usage in pig production [c]	2.8 (2.7-3.3)	2.0 (1.3-2.7)	2.2 (1.7-2.9)	2.7 (2.3-3.5)
Perceived risks of antimicrobial usage in pig production [c]	3.4 (3.0-4.0)	3.5 (2.7-4.1)	3.3 (2.7-4.0)	3.3 (2.7-4.0)
Perceived role of the veterinarian [c]	4.4 (3.8-5.0)	5.0 (4.4-5.3)	4.8 (4.1-5.4)	5.3 (4.9-5.9)
Perceived role of the feed expert [c]	2.1 (1.6-3.3)	3.8 (2.9-4.5)	1.9 (1.5-2.3)	1.3 (1.0-1.6)
Perceived impact of selected policy measures to reduce antimicrobial usage [c]	4.4 (3.8-4.8)	3.5 (2.9-4.5)	3.7 (3.1-4.5)	3.8 (2.8-4.5)
'I only administer antimicrobials to diseased pigs after having consulted my veterinarian' [d]	4.0 (2.3-5.0)	3.0 (2.0-5.0)	5.0 (3.0-5.8)	5.0 (4.0-6.0)
'All administrations of drugs are recorded and archived in my farm' [d]	4.0 (4.0-6.0)	5.1 (4.8-6.0)	6.0 (5.0-6.0)	6.0 (6.0-6.0)
***X_6* block : Farm technical performance**				
Number of litters per sow per year	2.38 (2.35-2.42)	2.47 (2.42-2.54)	2.37 (2.30-2.42)	2.20 (2.20-2.30)
Number of weaners per sow per year	26.2 (25.5-28.7)	26.2 (25.3-28.2)	26.9 (25.5-29.2)	23.6 (22.4-24.2)
Mortality in sucklers (%)	12.3 (10.1-14.9)	20.3 (16.9-23.8)	15.0 (11.5-17.5)	18.3 (15.6-20.9)

[a] For each sub-category of external and internal biosecurity practices, scores were attributed from 0 (=absence of biosecurity) to 100 (=very strict biosecurity) using the Biocheck.UGent™ scoring system (www.biocheck.ugent.be)

[b] Occurrence of clinical signs in each age group were based on farmer's indication of whether he/she had to treat his/her pigs because of given clinical signs (score from 1=never to 5 = every batch)

[c] Scores were measures on a scale from 1=very low to 6=very high

[d] Scores were measures on a scale from 1= does not apply to 6= fully applies

Principle of mbpls *analysis*

Data were analyzed using a *mbpls* analysis (Wold, 1984); the method, initially used in the field of chemometrics, sensometrics and process monitoring to explore the relationships between several datasets to be predicted from several other datasets, was recently adapted to the field of veterinary epidemiology (Bougeard et al. 2011; Bougeard et al., 2011b). Briefly, multiblock analyses are especially suitable when data are organized in (k+1) blocks of variables, consisting of a block of several variables to be explained **Y**, and a large number of explanatory variables, i.e. the potential risk factors, organized in k meaningful blocks ($\mathbf{X_1}$; . . . ; $\mathbf{X_k}$). All of these variables are being measured on the same epidemiological units.

Factor analysis is first performed to summarize the information contained in each block $\mathbf{X_k}$ into a limited number of partial components t_k.

$$t_k = \sum_i X_{ki}\, w_{ki} \qquad (1)$$

where k refers to the block's number and i to the variable's number within the block $\mathbf{X_k}$.

A global component t is then defined as a linear combination of the t_k; higher weights a_k are allocated to t_k explaining a bigger proportion of the variability in the block **Y**, and a_k verify the condition $\sum_k a_k^2 = 1$. The global component t therefore compiles the information provided by all explanatory variables.

$$t = \sum_k a_k t_k = \sum_k a_k X_k w_k = Xw \qquad (2)$$

Subsequently, q multivariable linear regression analyses are performed (q referring to the number of variables within the block **Y**), where each variable from the block **Y** is being explained by t.

$$\begin{cases} Y_1 = tc_1 + \mathcal{E}_1 \\ Y_2 = tc_2 + \mathcal{E}_2 \\ \ldots \\ Y_q = tc_q + \mathcal{E}_q \end{cases} \qquad (3)$$

where c is the regression coefficient of Y upon t and $\mathcal{E}$ represents the residuals of the regression models (Lupo et al., 2010; Bougeard et al., 2012).

Eq. (3) can be summarized as follows:

$$Y = tc + \mathcal{E} \qquad (4)$$

Combining Eq. (2) and Eq. (4), one can explore the direct relationship between the block **Y** and the explanatory variables of the blocks $\mathbf{X_k}$:

$$Y = Xwc + \mathcal{E} \qquad (5)$$

The description of the relationships between explanatory and response blocks via the use of partial and global components is presented in Figure 6.

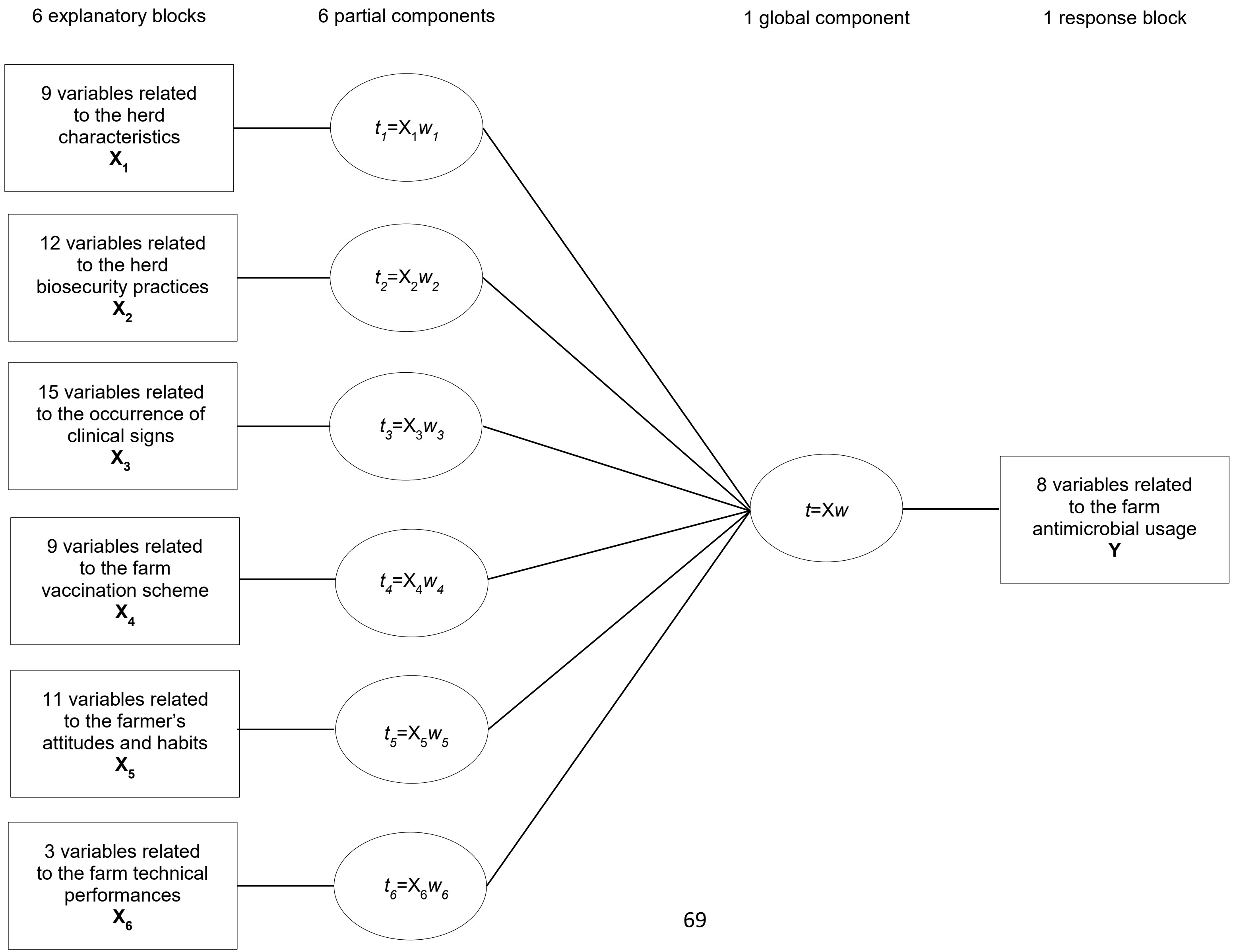


Figure 6. Conceptual scheme of the relationships between explanatory blocks ($\mathbf{X_1}$, …, $\mathbf{X_6}$) and the response block **Y**

To illustrate the method, the above procedure was described for a model with only one dimension (i.e. one partial component t_k for each block $\mathbf{X_k}$, and therefore one global component t). Depending on the complexity of the data, a multidimensional model can also be considered. The optimal number of dimensions to be retained is selected using a twofold cross-validation procedure with 500 repetitions; the choice is usually made as the best compromise between the fitting and prediction abilities of the model (Lupo et al., 2010).

Compared with traditional linear regression modeling, *mbpls* analysis presents three main advantages: i) it allows for multiple response variables to be studied simultaneously, ii) it is stable in case of multicollinearity within explanatory blocks (Westerhuis et al., 1998), iii) it allows not only to explore the associations between explanatory and response variables, but also between explanatory and response blocks of variables. Two interpretation tools called ‘variable importance index (VarImp)’ and ‘block importance index (BlockImp)’ are also available to describe, respectively, the relative contribution of each explanatory variable and each explanatory block to the explanation of the **Y** block (Bougeard et al., 2011b; Bougeard and Cardinal, 2014). If k is the number of explanatory blocks and p the total number of explanatory variables included in the model, VarImp and BlockImp indexes verify the properties: $\sum_p \mathrm{VarImp}_{\%} = 100\%$ and $\sum_k \mathrm{BlockImp}_{\%} = 100\%$. VarImp index can be used to simplify the model by selecting those variables with the highest contribution to the explanation of the **Y** block (Bougeard and Cardinal, 2014).

Application to the present study

The *mbpls* method was applied to the present study in order to achieve three objectives: i) describe the relative contribution of selected explanatory blocks of variables to the explanation of antimicrobial usage (block **Y**), ii) identify within each block, the factors mostly contributing to the explanation of antimicrobial usage (block **Y**), iii) explore whether these factors differ depending on the type of antimicrobial usage under study (i.e. age group, administration route and antimicrobial class as described by the different variables of the block **Y**). An initial, multicountry model was developed including the farm country of origin as an extra block; this block was explaining 33.0% (95% confidence interval (CI) 28.7-38.9) of the variation in the block **Y**. Because the country of origin was not the explanatory block of main interest, and because the relative contribution of the blocks $\mathbf{X_1}$ to $\mathbf{X_6}$, as well as the contribution of the variables within each block, were likely to significantly differ between countries, it was decided to rather develop four separate, country-specific models. Therefore, the relative contribution of each explanatory blocks and explanatory variables were explored for each country separately.

Data pre-processing

Several data transformation steps were required before performing the *mbpls* analysis. First, the *mbpls* approach did not allow for missing data to be present in the dataset. Twenty farms were therefore excluded from further analysis because data were missing for an entire block of explanatory variables (16 of them had not completed the questionnaire on attitudes and habits towards antimicrobial usage and had no data in the block $\mathbf{X_5}$). Thus, 207 farms, including 38 Belgian, 56 French, 54 German and 59 Swedish farms were included in the models. Remaining farms had sparse missing data for few variables (i.e. <3% of the farms); missing values were imputed using regularised iterative principal component and multiple correspondence analyses algorithms for quantitative and qualitative variables, respectively (Josse and Husson, 2012; Josse et al., 2012). Besides, variables of the block **Y** were normalized using logarithm transformation, after adding one to the original variable in order to adjust for zero values in the data. The categorical variable describing the herd farrowing rhythm had more than two classes and was converted into a dummy variable; a 3-week system was used as the reference class (as it is the most common farrowing system) and the corresponding dummy variable was removed to prevent redundancy in the dataset. As all the variables were expressed in different units, they were column centered and scaled to unit variance to give them the same weight in the analysis.

Preliminary study of the relationships between antimicrobial usage variables

Principal Component Analyses were first performed in each country-specific model to explore the relationships between the eight variables describing antimicrobial usage within the block **Y** (Abdi and Williams, 2010). At the difference of the blocks $\mathbf{X_k}$, multicollinearity between the variables of the block **Y** is desired as it increases the predictive power of the model (i.e. more similar outcomes have to be predicted).

Implementation of the mbpls *procedure*

Blocks $\mathbf{X_k}$, initially made of a total of 59 potential explanatory variables (Table 3), were defined and included in the model attributing equal weight to every variable in each block and equal weight to every block in the overall model (i.e. the weight of the block was independent from the number of variables in the block). The model with the best compromise between fitting and prediction abilities was obtained using one dimension in Belgium, France and Sweden, and two dimensions in Germany. The VarImp index of the full models (i.e. with 59 explanatory variables) were computed and following the parsimony principle, only those variables with a contribution >1% to the explanation of the block **Y** were retained in the final, reduced models. Statistical analyses were performed in the open-source environment R V.3.3.1 (R Core Team, 2016, www.r-project.org); missing values were imputed using the *missMDA* package, principal component analyses were performed using the *FactoMineR* package and *mbpls* analyses using the *ade4* package.

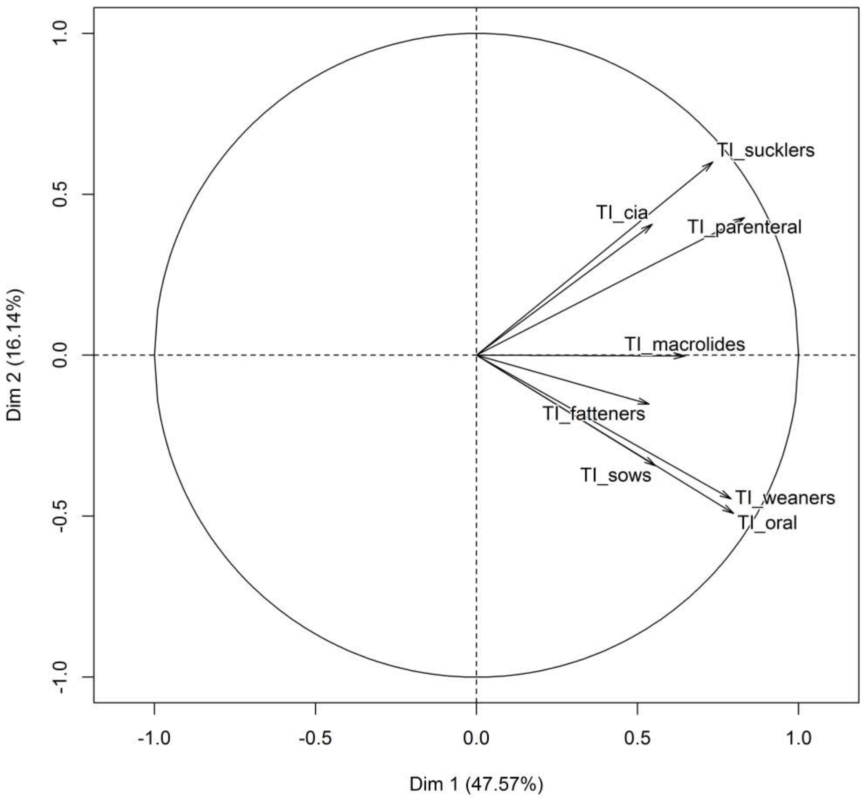
Interpretation of the final mbpls *models*

The BlockImp and VarImp indexes of the final models were then computed; k being the number of blocks $\mathbf{X_k}$ and p the number of explanatory variables included in the final model, blocks $\mathbf{X_k}$ verifying BlockImp>100/k and explanatory variables verifying VarImp>100/p (i.e. contribution higher than expected average contribution) were considered as significantly contributing to the explanation of the block **Y**. Additionally were estimated the regression coefficients β of the models linking explanatory variables to every variable of the block **Y**; the association was considered significant when the 95% confidence interval did not include zero. The estimation of the regression coefficients β was conducted only for the French model, as part of an exploratory analysis.

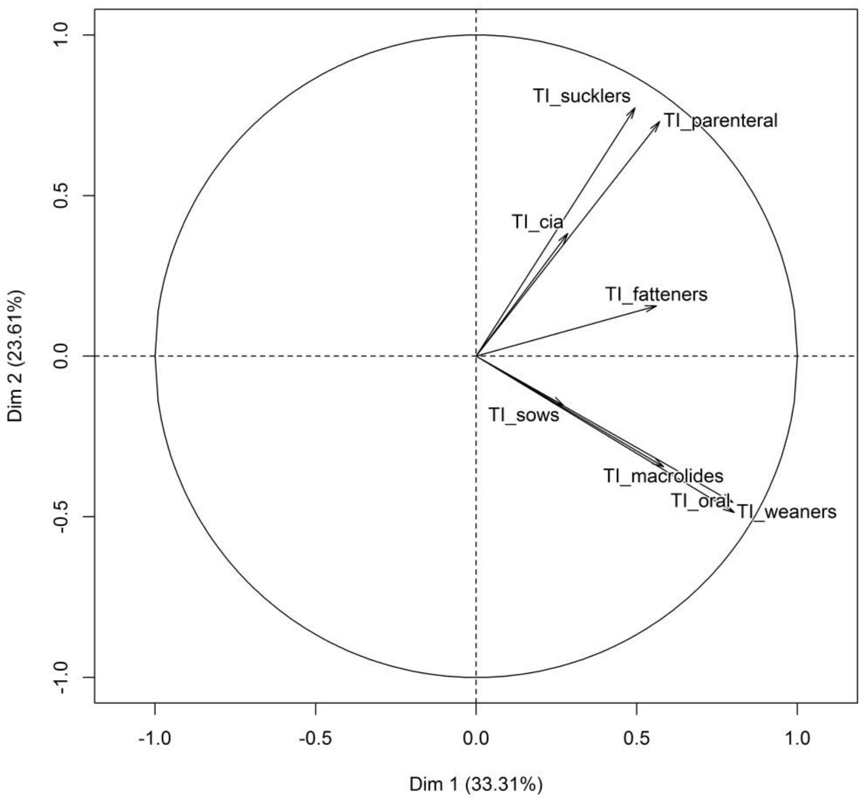
3.2.4 Results

Relationships between antimicrobial usage variables

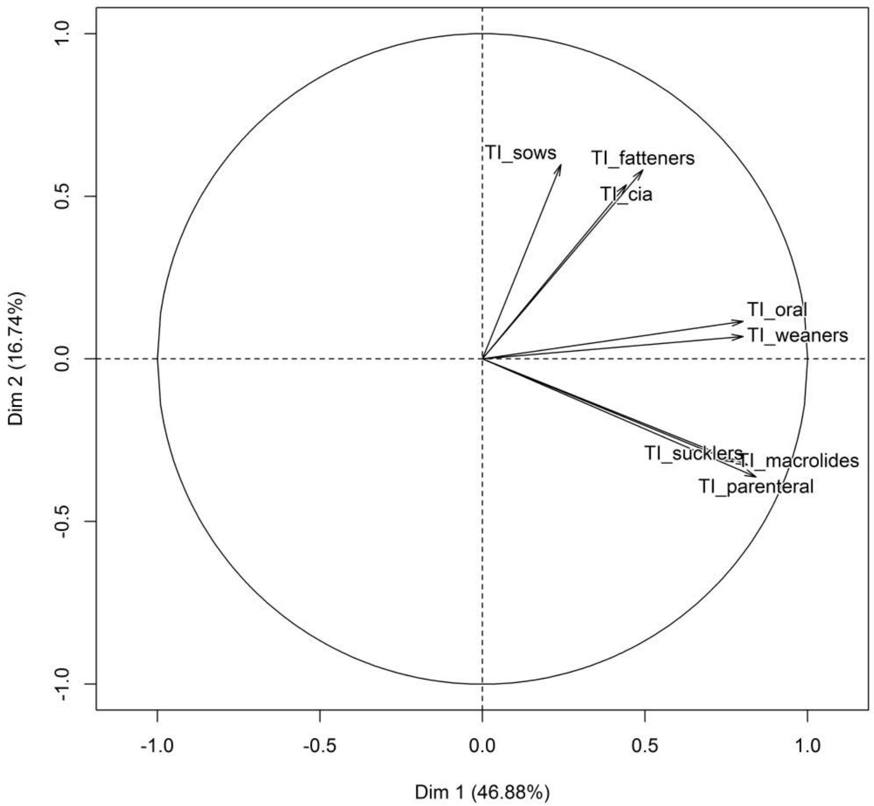
Figure 7 displays the results of the Principal Components Analyses performed among the **Y** block variables in each participating country. In each country, correlation was high between variables of the **Y** block. Especially treatment incidence via oral route was highly correlated with treatment incidence in weaners; this is because weaners are treated with antimicrobials mostly via feed or water routes (Sjölund et al., 2016). Treatment incidence via parenteral route was highly correlated with treatment incidence in sucklers in the four countries, and with treatment incidence in fatteners and sows in Sweden. Previous study showed that the proportion of antimicrobials administered via the parenteral route was higher in Sweden than in the three other countries (87% in Sweden versus 13 to 30% in the three other countries) (Sjölund et al., 2016). Treatment incidence with cephalosporins/fluoroquinolons was mostly correlated with treatment incidence in sucklers in Belgium and France (as already shown by (Sjölund et al., 2016)), and with treatment incidence in fatteners in Germany and Sweden; the latter might be related to the indication of fluoroquinolons for the control of *Actinobacillus pleuropneumoniae* (Damte et al., 2013).



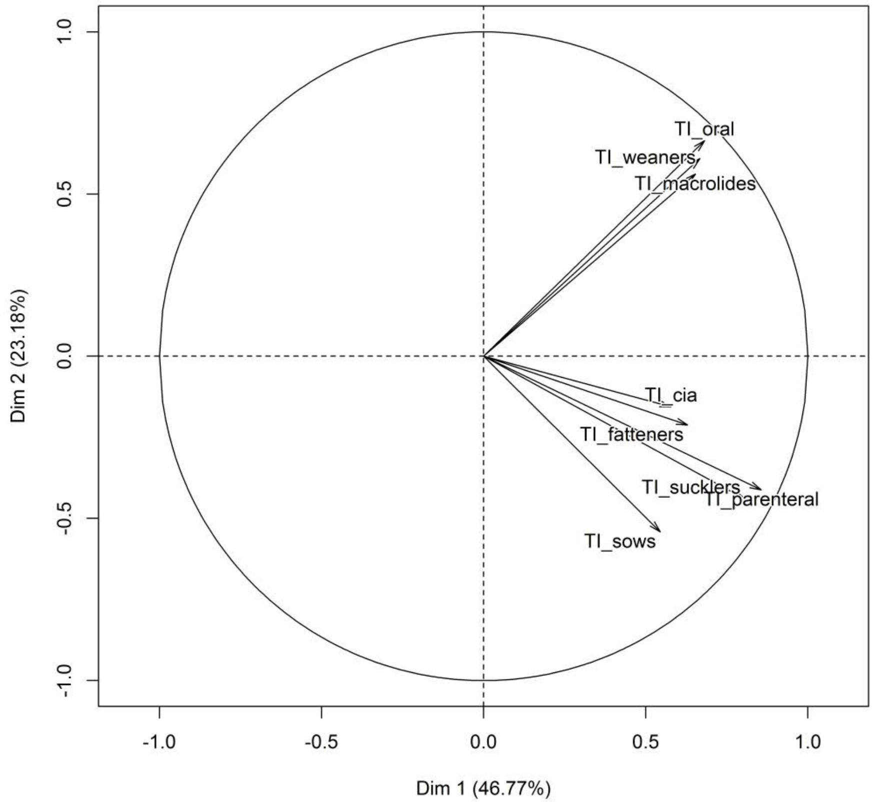
2.a Belgium (n=38 herds)



2.b France(n=56 herds)



2.c Germany (n=54 herds)



2.d Sweden (n=59 herds)

Figure 7. Circle of correlations of the block Y variables based on the components 1 and 2 of the Principal Components Analysis performed in each participating country

TI_sucklers: Log transformed treatment incidence in sucklers; TI_weaners: Log transformed treatment incidence in weaners; TI_fatteners: Log transformed treatment incidence in fatteners; TI_sows: Log transformed treatment incidence in sows/ gilts; TI_oral: Log transformed treatment incidence via oral route; TI_parenteral: Log transformed treatment incidence via parenteral route; TI_cia: Log transformed treatment incidence with cephalosporins/fluoroquinolons; TI_macrolides: Log transformed treatment incidence with macrolides

Relative contribution of explanatory blocks and explanatory variables to the explanation of antimicrobial usage

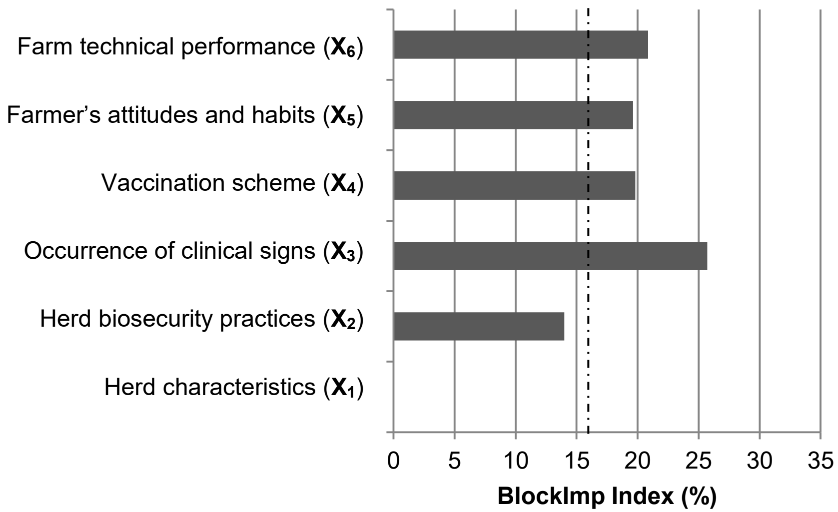
Figure 8 and Table 4 respectively present, in each participating country, the relative contribution of explanatory blocks $\mathbf{X_k}$ and explanatory variables to the explanation of antimicrobial usage (block **Y**). Overall, the contribution of the six selected explanatory blocks was relatively balanced in each country (Figure 8), and each block significantly contributed to explaining antimicrobial usage in at least one country. The occurrence of clinical signs (block $\mathbf{X_3}$) was one of the main contributors in all four models; Table 4 shows that this mostly related to the occurrence of respiratory signs in fatteners in Belgium, France and Germany, and to the occurrence of nervous signs in fatteners in Belgium and France. Occurrence of lameness in sows and metritis also had a significant contribution in France and Germany, respectively. The importance of the block $\mathbf{X_3}$ in Sweden was related to a rather small contribution of a diversity of clinical signs in all age groups. Observed associations were positive, meaning that the higher the occurrence of clinical signs, the higher the antimicrobial usage (Table 4).

Herd characteristics (block $\mathbf{X_1}$) was the main contributor in the German model; the higher the herd size and the lower the number of employees per 100 present sows, the higher the antimicrobial usage (Table 4). German herds with a 1-week or 2-week farrowing system also had higher antimicrobial usage compared with those having a 3-week system. Herd characteristics also contributed significantly to the Swedish model; especially herds with higher weaning age had lower antimicrobial usage. On the contrary, variables related to the herd characteristics had very small contribution in the Belgian model, and none of them was retained in the Belgian final model.

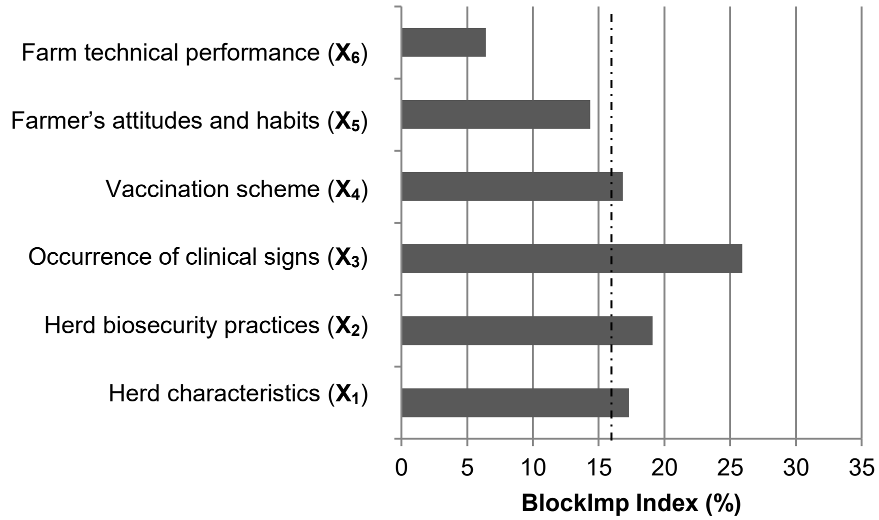
Similarly, variables related to the vaccination scheme (block $\mathbf{X_4}$) had very low contribution in the Swedish model and none of them were kept in the final model. This could be related to the fact that the proportion of herds implementing vaccination in Sweden was lower than in the other countries, especially against PRRS and influenza (see Table 3). PRRS vaccination had indeed a significant contribution in the Belgian and French models; vaccination against atrophic rhinitis and influenza were also significant in the Belgian and French model, respectively (Table 4).

Farmer’s attitudes and habits towards antimicrobial usage (block $\mathbf{X_5}$) significantly contributed to the Swedish and Belgian model, whereas no variable was kept in the German model. Belgian and Swedish farmers who attributed a higher score to ‘All administrations of drugs are recorded and archived in my farm’ had lower antimicrobial usage (Table 4). Swedish farmers with higher worries about AMR also had higher antimicrobial usage, whereas Belgian farmers with higher perceived risks of using antimicrobials had lower usage. Belgian farmers with higher worries about financial/legal issues also had higher usage.

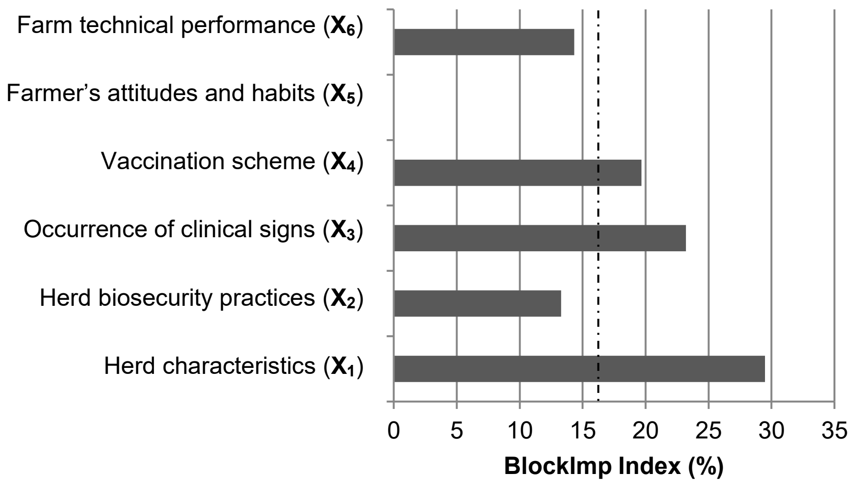
Biosecurity practices (block $\mathbf{X_2}$) mostly contributed to explaining antimicrobial usage in the French model. French farms that had better practices regarding water and feed supply, and that had more favorable locations (i.e. with reduced pig density) also had lower antimicrobial usage (Table 4). Farm technical performance (block $\mathbf{X_6}$) only had a significant contribution in the Belgian model (Figure 8); herds with more litters per sow per year and higher mortality in sucklers also had higher antimicrobial usage (Table 4).



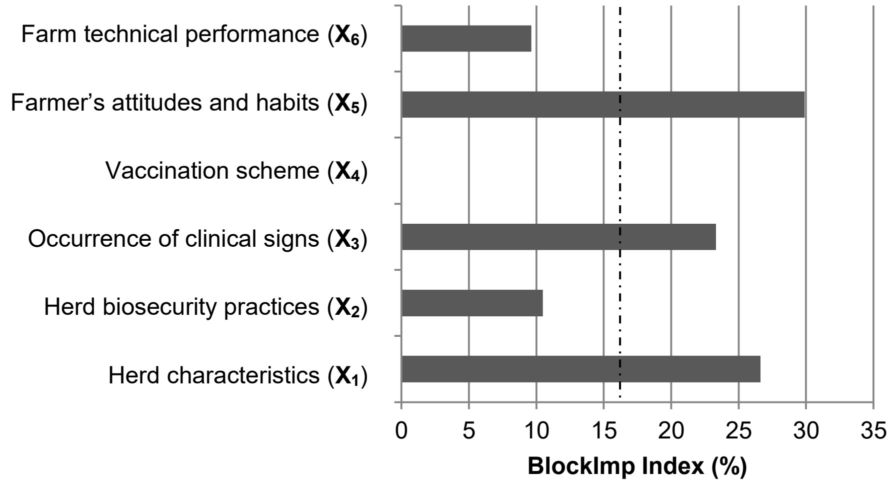
3.a Belgian model performed using one dimension and including 25 explanatory variables (n=38 herds)



3.b French model performed using one dimension and including 25 explanatory variables (n=56 herds)



3.c German model performed using two dimensions and including 25 explanatory variables (n=54 herds)



3.d Swedish model performed using one dimension and including 26 explanatory variables (n=59 herds)

Figure 8. Graphical representation of the BlockImp index of the explanatory blocks. Multiblock partial least squares (*mbpls*) analysis of farm antimicrobial usage (**Y**) explained by 6 blocks of variables: Herd characteristics ($\mathbf{X_1}$), Herd biosecurity practices ($\mathbf{X_2}$), Occurrence of clinical signs ($\mathbf{X_3}$), Vaccination scheme ($\mathbf{X_4}$), Farmer's attitudes and habits ($\mathbf{X_5}$) and Farm technical performance ($\mathbf{X_6}$). BlockImp index represents the relative contribution of each explanatory block to the explanation of antimicrobial usage (block **Y**) and verifies the condition $\sum_k \text{BlockImp}_{\%} = 100\%$ for k=1 to 6. Dash line represents the significance threshold (BlockImp>100/k). Blocks where BlockImp=0 are those for which no variable was kept in the block after the variable selection procedure.

Table 4. Variable Importance index of the reduced country-specific *mbpls* models and sign of the association between explanatory variable and antimicrobial usage (block **Y**)

	Belgium (n=38 herds)		France (n=56 herds)		Germany (n=54 herds)		Sweden (n=59 herds)	
	VarImp index (%)	Sign[a]	VarImp index (%)	Sign[a]	VarImp index (%)	Sign[a]	VarImp index (%)	Sign[a]
X_1 block : Herd characteristics								
Number of present sows	/		/		**7.0**	+	**4.7**	+
Number of employees per 100 present sows	/		/		**10.8**	-	/	
Farrowing system: 1- to 2-week system (vs 3-week)	/		/		**11.7**	+	/	
Farrowing system: 4- to 8-week system (vs 3-week)	/		**5.0**	-	3.5	-	**5.2**	-
Piglets weaning age	/		/		3.1	-	**14.0**	-
Farm using ZnO post-weaning	/		/		/		**6.2**	+
Experience with pig farming	/		**11.1**	+	/		/	
Highest education level of farm personnel	/		/		2.8	+	/	
X_2 block : Herd biosecurity practices								
Purchasing policy	0.8	-	/		1.7	-	0.7	-
Transport, elimination of manure and carcasses	2.0	-	2.2	-	1.9	-	0.5	-
Water and feed supply	0.7	-	**6.0**	-	/		0.9	-
Policy regarding farm visitors	1.3	+	1.3	-	2.4	-	0.3	-
Farm location	1.3	-	**5.6**	-	2.6	-	/	
Infectious diseases management	/		/		/		1.0	-
Management of the nursery unit	1.6	-	/		1.6	+	0.6	-
Management of the fattening unit	/		2.3	-	/		/	
Farm compartmentation	/		2.1	-	/		0.6	-
Cleaning and disinfection	1.8	-	/		/		/	
X_3 block : Occurrence of clinical signs								
Occurrence of lameness in sucklers	/		/		**4.7**	+	3.5	+
Occurrence of gastro-intestinal in sucklers	/		/		/		1.5	+
Occurrence of respiratory signs in sucklers	/		/		/		1.7	+
Occurrence of lameness in weaners	/		/		**4.6**	+	/	
Occurrence of gastro-intestinal in weaners	3.0	+	/		/		3.8	+
Occurrence of respiratory signs in weaners	2.2	+	/		/		1.8	+
Occurrence of nervous signs in weaners	2.4	+	/		/		0.9	+

Occurrence of gastro-intestinal in fatteners	/		**5.0**	+	/		**4.1**	+
Occurrence of respiratory signs in fatteners	**5.9**	+	**15.5**	+	**6.0**	+	1.7	+
Occurrence of nervous signs in fatteners	**4.8**	+	**4.1**	+	/		/	
Occurrence of lameness in sows	/		**11.4**	+	/		/	
Occurrence of respiratory signs in sows	**8.1**	+	/		/		0.7	+
Occurrence of metritis in sows	2.5	+	/		**8.9**	+	1.7	+
Occurrence of mastitis in sows	3.2	+	/		/		1.8	+
X_4 block : Vaccination scheme								
Vaccination against porcine parvovirus: yes (vs no)	3.9	-	/		/		/	
Vaccination against *Escherichia coli*: yes (vs no)	/		/		**4.5**	+	/	
Vaccination against *Clostridium spp*: yes (vs no)	2.3	+	**5.9**	+	2.0	+	/	
Vaccination against atrophic rhinitis: yes (vs no)	**4.4**	+	/		1.3	+	/	
Vaccination against PRRS virus: yes (vs no)	**8.4**	+	**5.1**	+	1.8	+	/	
Vaccination against influenza virus: yes (vs no)	/		**4.2**	+	2.5	+	/	
Vaccination against *Mycoplasma hyopneumoniae*: yes (vs no)	/		/		3.0	-	/	
Vaccination against *Actinobacillus pleuropneumoniae*: yes (vs no)	/		/		2.6	+	/	
X_5 block : Farmer's attitudes and habits								
Worries about infectious diseases in his/her pigs	/		1.1	-	/		/	
Worries about antimicrobial resistance	/		3.8	-	/		**25.4**	+
Worries about financial/legal issues	**5.4**	+	/		/		/	
Perceived benefits of antimicrobial usage in pig production	/		1.4	+	/		/	
Perceived need for antimicrobial usage in pig production	/		1.8	+	/		/	
Perceived risks of antimicrobial usage in pig production	**7.8**	-	1.0	-	/		/	
Perceived role of the feed expert	/		1.0	-	/		/	
'All administrations of drugs are recorded and archived in my farm'	**5.4**	-	0.9	-	/		**12.7**	-
X_6 block : Farm technical performance								
Number of litters per sow per year	**8.4**	+	0.1	+	0.9	+	/	
Number of weaners per sow per year	0.7	-	0.7	+	**5.5**	-	2.3	+
Mortality in sucklers	**11.9**	+	1.4	-	2.9	+	1.6	-

VarImp index represents the relative contribution of each explanatory variable to the explanation of antimicrobial usage (block **Y**) and verifies the condition $\sum_p VarImp_{\%} = 100\%$, p being the number of explanatory variables (p=25 for Belgium, France and Germany, and p=26 for Sweden). The slash sign means the variable was not kept in the country-specific model after the variable selection procedure. VarImp highlighted in bold are those higher than 100/p (significance threshold).

[a] The sign of the association was provided by the sign of the regression coefficients β of the models linking explanatory variables to every variable of the block Y

Association between explanatory variables and individual variables describing antimicrobial usage: exploratory study based on the French model

While Table 4 provided the VarImp index, i.e. the relative contribution of each explanatory variable to the explanation of the block **Y** as a whole, the associations between explanatory variables and individual variables of the block **Y** may vary. This is because variables of the block **Y** are strongly but not 100% correlated (see Figure 7). The *mbpls* method allows for the association between every explanatory variable and every individual variables of the block **Y** to be explored via the estimation of the regression coefficients *β*; the results of the French model are provided in Table 5 as part of an exploratory analysis.

Significant risk factors were observed to be associated with treatment incidence in weaners and treatment incidence via the oral route. Ten risk factors were common to these two outcome variables; this is not surprising as the treatment incidence in weaners and via the oral route were highly correlated (Figure 7). On the contrary, no risk factor appeared to be significantly associated with treatment incidence in sucklers, treatment incidence in sows/gilts, treatment incidence via the parenteral route or with cephalosporins /fluoroquinolons.

Table 5 shows that farmers with bigger experience with pig farming had higher treatment incidence in weaners and via the oral route, and higher treatment incidence in fatteners. Additionally, farms with higher external biosecurity (especially in relation with transport/elimination of manure/carcasses, supply of water/feed and farm location) and higher internal biosecurity (especially in relation with the management of the fattening unit and the farm compartmentation) had lower antimicrobial usage in weaners and via the oral route. Farms with higher occurrence of gastro-intestinal, respiratory and nervous signs in fatteners as well as higher occurrence of lameness in sows had higher treatment incidence in weaners and via the oral route. Farms vaccinating against *Clostridium spp*, PRRS virus and influenza virus also had high treatment incidence in weaners. Farmers with higher worries about AMR had lower treatment incidence in weaners and via the oral route, and had lower usage of macrolides, whereas those who perceived a major role of their feed expert to assist them in reducing antimicrobial usage had lower usage in weaners.

Regression coefficients of the explanatory variables related to the antimicrobial usage variables obtained with mbpls analysis: exploratory study based on the French model

Table 5. Regression coefficients of the explanatory variables related to the outcome variables of the block Y in the French model (n=56 herds)

	log TI sucklers		log TI weaners		log TI fatteners		log TI sows	
	β	95% CI	*β*	95% CI	*β*	95% CI	*β*	95% CI
X_1 block : Herd characteristics								
Farrowing system: 4- to 8-week system (vs 3-week)	-0.03	-0.12 ; 0.12	-0.15	-0.44 ; 0.00	-0.06	-0.19 ; 0.04	-0.04	-0.14 ; 0.05
Experience with pig farming	0.05	-0.05 ; 0.32	**0.22**	**0.07 ; 0.52**	**0.09**	**0.01 ; 0.27**	0.06	-0.04 ; 0.19
X_2 block : Herd biosecurity practices								
Transport, elimination of manure and carcasses	-0.02	-0.11 ; 0.06	**-0.09**	**-0.22 ; -0.01**	-0.04	-0.09 ; 0.05	-0.02	-0.06 ; 0.05
Water and feed supply	-0.03	-0.13 ; 0.08	**-0.16**	**-0.34 ; -0.08**	-0.06	-0.13 ; 0.04	-0.04	-0.09 ; 0.04
Policy regarding farm visitors	-0.02	-0.08 ; 0.05	-0.07	-0.18 ; 0.03	-0.03	-0.08 ; 0.04	-0.02	-0.06 ; 0.03
Farm location	-0.03	-0.15 ; 0.06	**-0.15**	**-0.31 ; -0.07**	-0.06	-0.13 ; 0.04	-0.04	-0.10 ; 0.03
Management of the fattening unit	-0.02	-0.10 ; 0.05	**-0.10**	**-0.21 ; -0.01**	-0.04	-0.09 ; 0.03	-0.02	-0.07 ; 0.02
Farm compartmentation	-0.02	-0.09 ; 0.07	**-0.09**	**-0.25 ; -0.02**	-0.04	-0.10 ; 0.03	-0.02	-0.06 ; 0.04
X_3 block : Occurrence of clinical signs								
Occurrence of gastro-intestinal in fatteners	0.03	-0.06 ; 0.15	**0.12**	**0.04 ; 0.28**	0.05	-0.02 ; 0.12	0.03	-0.05 ; 0.09
Occurrence of respiratory signs in fatteners	0.05	-0.05 ; 0.22	**0.22**	**0.12 ; 0.40**	0.09	-0.01 ; 0.18	0.05	-0.02 ; 0.15
Occurrence of nervous signs in fatteners	0.02	-0.10 ; 0.09	**0.11**	**0.02 ; 0.27**	0.05	-0.02 ; 0.11	0.03	-0.05 ; 0.08
Occurrence of lameness in sows	0.04	-0.11 ; 0.13	**0.18**	**0.08 ; 0.43**	0.08	-0.03 ; 0.17	0.05	-0.05 ; 0.11
X_4 block : Vaccination scheme								
Vaccination against *Clostridium spp*: yes (vs no)	0.03	-0.05 ; 0.25	**0.17**	**0.01 ; 0.38**	0.07	-0.03 ; 0.18	0.04	-0.04 ; 0.17
Vaccination against PRRS virus: yes (vs no)	0.03	-0.07 ; 0.19	**0.15**	**0.00 ; 0.36**	0.06	-0.06 ; 0.15	0.04	-0.06 ; 0.13
Vaccination against influenza virus: yes (vs no)	0.03	-0.13 ; 0.09	**0.14**	**0.03 ; 0.36**	0.06	-0.06 ; 0.14	0.03	-0.07 ; 0.09
X_5 block : Farmer's attitudes and habits								
Worries about infectious diseases in his/her pigs	-0.02	-0.06 ; 0.07	-0.08	-0.21 ; 0.00	-0.03	-0.09 ; 0.05	-0.02	-0.06 ; 0.03
Worries about antimicrobial resistance	-0.03	-0.15 ; 0.05	**-0.14**	**-0.28 ; -0.08**	-0.06	-0.12 ; 0.02	-0.04	-0.10 ; 0.02
Perceived benefits of antimicrobial usage in pig production	0.02	-0.04 ; 0.09	0.09	0.00 ; 0.20	0.04	-0.04 ; 0.09	0.02	-0.04 ; 0.06
Perceived need for antimicrobial usage in pig production	0.02	-0.11 ; 0.05	0.10	0.00 ; 0.27	0.04	-0.06 ; 0.11	0.02	-0.05 ; 0.07
Perceived risks of antimicrobial usage in pig production	-0.02	-0.06 ; 0.06	-0.07	-0.20 ; 0.02	-0.03	-0.09 ; 0.04	-0.02	-0.06 ; 0.02
Perceived role of the feed expert	-0.02	-0.06 ; 0.05	**-0.07**	**-0.18 ; -0.01**	-0.03	-0.07 ; 0.02	-0.02	-0.05 ; 0.03
'All administrations of drugs are recorded and archived in my farm'	-0.02	-0.05 ; 0.08	-0.07	-0.21 ; 0.03	-0.03	-0.08 ; 0.05	-0.02	-0.06 ; 0.05
X_6 block : Farm technical performance								
Number of litters per sow per year	0.01	-0.14 ; 0.06	0.04	-0.13 ; 0.23	0.02	-0.13 ; 0.09	0.01	-0.07 ; 0.07
Number of weaners per sow per year	0.02	-0.14 ; 0.07	0.09	-0.04 ; 0.33	0.04	-0.05 ; 0.14	0.02	-0.07 ; 0.11
Mortality in sucklers	-0.03	-0.13 ; 0.06	-0.13	-0.28 ; -0.04	-0.05	-0.12 ; 0.03	-0.03	-0.09 ; 0.04

	log TI oral		log TI parenteral		log TI cephalosporins /fluoroquinolons		log TI macrolides	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
X_1 block : Herd characteristics								
Farrowing system: 4- to 8-week system (vs 3-week)	**-0.14**	**-0.42 ; -0.01**	-0.05	-0.14 ; 0.10	-0.01	-0.08 ; 0.10	-0.08	-0.26 ; 0.00
Experience with pig farming	**0.21**	**0.07 ; 0.48**	0.08	-0.02 ; 0.37	0.01	-0.11 ; 0.12	0.12	-0.01 ; 0.28
X_2 block : Herd biosecurity practices								
Transport, elimination of manure and carcasses	-0.09	-0.20 ; 0.00	-0.03	-0.13 ; 0.04	0.00	-0.06 ; 0.05	-0.05	-0.12 ; 0.02
Water and feed supply	**-0.15**	**-0.31 ; -0.06**	-0.06	-0.16 ; 0.05	-0.01	-0.07 ; 0.08	**-0.08**	**-0.19 ; -0.01**
Policy regarding farm visitors	-0.07	-0.17 ; 0.04	-0.03	-0.10 ; 0.05	0.00	-0.05 ; 0.05	-0.04	-0.10 ; 0.04
Farm location	**-0.14**	**-0.29 ; -0.04**	-0.05	-0.19 ; 0.04	-0.01	-0.11 ; 0.05	-0.08	-0.17 ; 0.01
Management of the fattening unit	**-0.09**	**-0.19 ; -0.01**	-0.03	-0.12 ; 0.04	0.00	-0.03 ; 0.07	-0.05	-0.12 ; 0.00
Farm compartmentation	-0.09	-0.23 ; 0.01	-0.03	-0.10 ; 0.05	0.00	-0.03 ; 0.08	-0.05	-0.14 ; 0.02
X_3 block : Occurrence of clinical signs								
Occurrence of gastro-intestinal in fatteners	**0.11**	**0.03 ; 0.26**	0.04	-0.04 ; 0.17	0.01	-0.06 ; 0.08	0.07	-0.03 ; 0.15
Occurrence of respiratory signs in fatteners	**0.20**	**0.10 ; 0.37**	0.08	-0.02 ; 0.28	0.01	-0.07 ; 0.14	**0.12**	**0.02 ; 0.23**
Occurrence of nervous signs in fatteners	**0.10**	**0.01 ; 0.25**	0.04	-0.10 ; 0.11	0.01	-0.05 ; 0.06	0.06	-0.01 ; 0.16
Occurrence of lameness in sows	**0.17**	**0.06 ; 0.39**	0.07	-0.08 ; 0.16	0.01	-0.07 ; 0.10	0.10	0.00 ; 0.23
X_4 block : Vaccination scheme								
Vaccination against *Clostridium spp: yes (vs no)*	0.15	0.00 ; 0.35	0.06	-0.03 ; 0.28	0.01	-0.09 ; 0.10	0.09	-0.04 ; 0.20
Vaccination against PRRS virus: yes (vs no)	0.14	-0.02 ; 0.34	0.05	-0.04 ; 0.24	0.01	-0.05 ; 0.14	0.08	-0.05 ; 0.19
Vaccination against influenza virus: yes (vs no)	**0.13**	**0.02 ; 0.34**	0.05	-0.12 ; 0.12	0.01	-0.07 ; 0.07	0.08	-0.01 ; 0.21
X_5 block : Farmer's attitudes and habits								
Worries about infectious diseases in his/her pigs	-0.07	-0.20 ; 0.01	-0.03	-0.08 ; 0.07	0.00	-0.03 ; 0.05	-0.04	-0.12 ; 0.02
Worries about antimicrobial resistance	**-0.13**	**-0.26 ; -0.06**	-0.05	-0.18 ; 0.04	-0.01	-0.06 ; 0.06	**-0.08**	**-0.15 ; -0.01**
Perceived benefits of antimicrobial usage in pig production	0.08	-0.01 ; 0.19	0.03	-0.03 ; 0.10	0.00	-0.06 ; 0.04	0.05	-0.02 ; 0.11
Perceived need for antimicrobial usage in pig production	0.09	0.00 ; 0.25	0.04	-0.11 ; 0.08	0.01	-0.06 ; 0.05	0.05	-0.02 ; 0.16
Perceived risks of antimicrobial usage in pig production	-0.07	-0.19 ; 0.02	-0.03	-0.08 ; 0.05	0.00	-0.04 ; 0.04	-0.04	-0.11 ; 0.01
Perceived role of the feed expert	-0.07	-0.17 ; 0.00	-0.03	-0.07 ; 0.04	0.00	-0.03 ; 0.04	-0.04	-0.10 ; 0.01
'All administrations of drugs are recorded and archived in my farm'	-0.07	-0.20 ; 0.03	-0.03	-0.07 ; 0.07	0.00	-0.03 ; 0.08	-0.04	-0.12 ; 0.04
X_6 block : Farm technical performance								
Number of litters per sow per year	0.04	-0.13 ; 0.21	0.01	-0.15 ; 0.08	0.00	-0.04 ; 0.06	0.02	-0.10 ; 0.13
Number of weaners per sow per year	0.08	-0.04 ; 0.32	0.03	-0.12 ; 0.09	0.00	-0.07 ; 0.06	0.05	-0.04 ; 0.20
Mortality in sucklers	**-0.12**	**-0.27 ; -0.01**	-0.05	-0.16 ; 0.03	-0.01	-0.10 ; 0.04	-0.07	-0.16 ; 0.02

β coefficients highlighted in bold are those for which the association is significant (i.e. CI95% does not contain zero).

3.2.5 Discussion

The relative importance of selected drivers for antimicrobial usage in farrow-to-finish pig production was explored using an innovative analytical approach called *mbpls*. To our knowledge, this is the first study that included into the same model and across four countries both technical (i.e. herd characteristics, biosecurity level, occurrence of clinical signs and vaccination scheme) and psychosocial drivers (i.e. farmer's attitudes and habits towards antimicrobial usage) organized in meaningful categories or 'blocks' of explanatory variables. The *mbpls* analysis showed that the contribution of the six selected explanatory blocks was relatively balanced in each country, and each block significantly contributed to explaining antimicrobial usage in at least one country. It means that antimicrobial usage in pig production is influenced simultaneously by a wide range of drivers, and that the reduction of antimicrobial in pigs should be addressed following a holistic approach, as recommended by national and European action plans against AMR (European Commission, 2011).

The occurrence of clinical signs was one of the main drivers for antimicrobial usage in all four countries; it suggests that participating farms mostly relied on antimicrobials for metaphylactic and curative treatments, i.e. treatment of clinically sick animals (Anses, 2014). This is agreement with the current revision of EU Directive 90/167/EEC that proposes to introduce a ban of the preventive use of medicated feed containing antimicrobials in food-producing animals (European Commission, 2014). The in-depth study of the contribution of individual variables within the block 'occurrence of clinical signs' showed that especially the occurrence of respiratory signs in fatteners significantly contributed to antimicrobial usage in Belgium, France and Germany. This is in accordance with other research that showed that farms with fewer respiratory signs in fatteners had lower antimicrobial usage and better technical performance (see Chapter 4). Herds vaccinating against PRRS in Belgium and France, and against influenza in France had higher antimicrobial usage, suggesting that farms affected by these respiratory diseases used a combination of vaccination and antimicrobials to control them. The occurrence of nervous signs in fatteners also significantly contributed to antimicrobial usage in Belgium and France; it could be explained by an increased susceptibility to *Streptococcus suis*, known to be promoted by co-infection with PRRS (Thanawongnuwech et al., 2000). Occurrence of lameness in sows also had a significant contribution in France; it could be related to the recent implementation of group housing in sows (European Commission, 2008), that could have led to an increase need for antimicrobials treatments, as previously suggested by Hémonic et al. (2016). Occurrence of metritis was also identified as a main driver for antimicrobial usage in Germany, as already shown by van Rennings et al. (2015).

Non-medical drivers also played a role in explaining antimicrobial usage, especially herd size, farrowing rhythm and weaning age, as well as increased biosecurity, as already shown in previous studies (Postma et al., 2016; Backhans et al., 2016). Systems with longer between-farrowing periods are known to facilitate the implementation of a strict all-in all-out management of pig batches. Farm technical performance significantly contributed to explaining antimicrobial usage in Belgium, but had a limited contribution in other countries. It could partly be explained by the limited number of variables included in this block (especially growth performance were missing), and by the cross-sectional design of the study, preventing the interpretation of the temporal association between antimicrobial usage and performance. Farmer's attitudes and habits towards antimicrobial usage significantly contributed to the Belgian and Swedish models, but not to the German model. It might be related to the fact the Germany has large, integrated pig farms where treatment procedures are likely to be more standardized (Schulze, 2006).

An exploratory study was later conducted using the French data to investigate whether identified risk factors depended on the type of antimicrobial usage (i.e. age group, administration route, antimicrobial class) under study. Observed risk factors mostly related to treatment incidence in weaners and via the oral route, but no risk factor appeared to be significantly associated with treatment incidence in sucklers, treatment incidence in sows/gilts, treatment incidence via the parenteral route or with cephalosporins /fluoroquinolons, and only few risk factors were associated with treatment incidence in fatteners and treatment incidence with macrolides. This could be because treatment incidence was generally low in those categories of usage; Sjölund et al. (2016) showed that treatment incidence in sucklers (median: 12.9, CI95%: 0.0–637.7) and in sows/gilts (median: 0.7, CI95%: 0.0–382.5) was low compared to treatment incidence in weaners (median: 320.1, CI95%: 0.0–1794.6). Similarly, parenteral treatments and treatments with cephalosporins /fluoroquinolons only represented 13% and 1.6% of total treatment incidence in French herds, respectively (Sjölund et al., 2016). Because of this special distribution of antimicrobial treatment practices in France, with most treatments being administered to weaners and via the oral route, the *mbpls* approach did not really help to allocate risk factors to different categories of antimicrobial usage. However, it would be interesting to explore this further by developing a similar approach in the other MINAPIG participating countries. Besides, splitting treatment incidence and selected risk factors per age group made some associations difficult to interpret, e.g. when occurrence of clinical signs in fatteners was shown to be associated with treatment incidence in weaners; we cannot exclude however, that farmers used antimicrobial treatments in weaners to prevent future occurrence of clinical signs during the fattening period.

Still, the use of the *mbpls* approach made it possible to quantify the relative contribution of selected explanatory variables and explanatory blocks to the explanation of antimicrobial usage in the four participating countries. The VarImp and BlockImp indexes were therefore useful to rank selected explanatory variables and blocks of variables, and to identify those explanatory blocks and variables which contribution was higher than a defined threshold. However, they did not provide information on the absolute significance of explanatory variables; the latter was provided by computing the regression coefficients β with individual response variables. The overall significance of the model might therefore be low. Also sample size of country-specific models was rather small. It was initially planned to develop a multi-country model but the major effect observed for the variable describing the herd's country of origin showed this was not a relevant approach (i.e. including the country of origin would have 'erased' the effect of the other blocks of interest), and that antimicrobial usage could be influenced by different drivers in each participating country. At this stage, it is not possible to control for confounding in a *mbpls* model, but this feature is currently under development.

To conclude, by identifying the main drivers and categories of drivers mostly influencing antimicrobial usage in each participating country, this study provided a basis for the prioritization of future strategies to mitigate the risk associated with antimicrobial usage in pig production. Because several categories of drivers were shown to influence antimicrobial usage, a holistic risk mitigation strategy is highly recommended.

3.2.6 Acknowledgments

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3.3 Conclusion of the chapter

Strategies aiming at mitigating the risk arising from antimicrobial usage in food producing animals encourage the responsible and reduced use of antimicrobials. For these strategies to be successful, it is critical to understand why antimicrobials are used in the first place. In Chapter 3, it was shown that herd characteristics, biosecurity level, farm performance, occurrence of clinical signs, vaccination scheme and farmer's attitudes and habits towards antimicrobial usage all partially contribute to explain the use of antimicrobials in pig production. These results support the holistic approach that has been promoted so far by international, European and national action plans to tackle AMR.

While occurrence of clinical signs was one of the main contributors to the explanation of antimicrobial usage in all four participating countries, the relative contribution of the other categories of drivers differed from one country to another. These country-specific features should therefore be considered when prioritizing future risk mitigation activities.

CHAPTER 4: PROFILE OF PIG FARMS COMBINING HIGH TECHNICAL PERFORMANCE AND LOW ANTIMICROBIAL USAGE

4.1 Chapter introduction

Chapter 3 showed that technical performance significantly contributed to explain the use of antimicrobials in a herd. However, the observed direction of change was not consistent between countries or between technical variable. Indeed, the direction of change is difficult to interpret, especially in a cross-sectional study where the temporality between exposure (i.e. technical performance) and outcome (i.e. antimicrobial usage) is unknown. Farms with high performance can either have low antimicrobial usage in case they have very high health status with few clinical signs, or high antimicrobial usage in case they do have health problems but are using antimicrobials to control them.

To explore further this idea, it was decided to develop a logistic regression model to describe the profile of those farms that managed to have both high technical performance and low antimicrobial usage, i.e. investigating how they differed from other farms in terms of herd characteristics, biosecurity level, pig health and vaccination scheme.

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4.2 Publication

Profile of pig farms combining high performance and low antimicrobial usage within four European countries

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Adapted from:

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4.2.1 Abstract

Because of the rising threat from antimicrobial resistance, pig farmers are strongly encouraged to reduce their antimicrobial usage. However, such efforts should not compromise the heard health status and performance. This study aimed at describing the profile of so called 'top-farms' that managed to combine both high technical performance and low antimicrobial usage. A cross-sectional study was conducted among 227 farrow-to-finish farms in Belgium, France, Germany and Sweden. Among them, 44 farms were allocated to the top-farms group and were compared to the 'regular' farms group in terms of farm characteristics, biosecurity and health status.

Top-farms had fewer gastro-intestinal signs in suckling pigs and fewer respiratory signs in fatteners, which could partly explain their reduced need for antimicrobials and higher performance. They also had higher biosecurity and were located in sparsely populated pig areas. However, fourteen farms of the top-farms group were located in densely populated pig areas, but still managed to have low usage and high technical performance; they had higher internal biosecurity and more extensive vaccination against respiratory pathogens. These results illustrate that it is possible to control infectious diseases using other approaches than high antimicrobial usage, even in farms with challenging environmental and health conditions.

Keywords*:* antibiotics, biosecurity, health management

4.2.2 Introduction

The development and spread of antimicrobial resistance has been related, among other factors, to the use of antimicrobials in food producing animals (ECDC, EFSA and EMA, 2015). Therefore, livestock farmers are strongly encouraged to reduce their antimicrobial usage (European Commission 2011). However, this should not compromise the herd health status or the farm's technical and economic performance (Rojo-Gimeno et al., 2016). Pig farms located in densely populated livestock areas are particularly at risk of introducing infectious (especially respiratory) diseases (Rose and Madec 2002 ; Nathues et al., 2014). Some studies have investigated the link between antimicrobial usage and farm technical or economic performance; they did not find any significant associations between them (Chauvin et al., 2005 ; van der Fels-Klerx et al., 2011). This means that farms with high technical performance can have low to high levels of antimicrobial usage; it also means that some 'top-farms' manage to combine both high technical performance and low antimicrobial usage. This raises the question of what herd characteristics or farm management practices could potentially distinguish these top-farms from the others.

Previous research has shown that the main drivers for antimicrobial usage include the herd health status (Hughes et al., 2008), the farm practices and technical characteristics, e.g. biosecurity (Laanen et al., 2013; Postma et al., 2016a) as well as the farmers' perceptions, attitudes and behaviors regarding antimicrobial usage and resistance (Coyne et al., 2014 ; Visschers et al., 2015). Belgium, France, Germany and Sweden have different pig production systems (Marquer et al., 2014). They also differ substantially in terms of antimicrobial treatment practices in animals (European Medicines Agency 2015; Sjölund et al., 2016). The objective of this study was to describe, across these four countries, the profile of farrow-to-finish pig farms that are capable of combining both high technical performance and low antimicrobial usage. By focusing on this particular sub-population, we thoroughly explored how these top-farms differed from the others in terms of herd characteristics, biosecurity level and health management. This study was conducted as part of the MINAPIG Emida Era-Net project that aims to evaluate strategies for raising pigs with minimal antimicrobial usage.

4.2.3 Materials and methods

Study design

A cross-sectional study was conducted among a convenience sample of 227 farrow-to-finish pig farms located in Belgium (*n* = 47), France (*n* = 60), Germany (*n* = 60) and Sweden (*n* = 60) between December 2012 and January 2014. In Belgium, volunteer farmers were recruited among those subscribing to a newsletter issued by the faculty of veterinary medicine of Ghent University; for logistics reasons, only farms located in the Flanders region, which represents 90% of Belgium pig production, were included (Statistics Belgium, 2013). French herds were randomly selected from a database of the Institute for pig and pork industry among those located in the north-western part of France, representing 75% of the national pig production (French Institute for pig and pork industry 2013). In Germany, herds were recruited from the three regions with the largest pig production, i.e. Niedersachsen, Nordrhein-Westfalen and Mecklenburg-Vorpommern covering 64% of total German production (Statistisches Bundesamt 2013), using consultancy circles and input from herd veterinarians. Swedish farmers were recruited via direct request for participation by their herd veterinarian or a project consortium partner. Initial inclusion criterion was the presence of more than 100 sows; it was later lowered to 70 sows to reach the maximum of participating herds. Three Belgian herds, six French herds and one Swedish herd had a number of sows between 70 and 100.

Each participating herd was visited by one investigator (i.e. veterinary researcher) in Belgium, one in France and one in Germany and by two researchers or a veterinarian from the Swedish Animal Health Service in Sweden. A detailed protocol was prepared and investigators received training to harmonize data collection and entry across the four countries. Collected data related to antimicrobial consumption, herd characteristics and technical performance, as well as the biosecurity and health status.

Antimicrobial consumption

Data on antimicrobial usage in suckling piglets, weaners and finishers (including commercial product name, formulation and concentration, amount purchased or used, targeted animal category and routine versus non routine administration) were collected over one year preceding the visit in Belgium, Germany and Sweden, and over the last batch produced at the moment of the visit in France (see (Sjölund et al., 2016) for more details on data collection). Data were collected using invoices of veterinarians and feed companies in Belgium, and delivery and treatment forms of the prescribing herd veterinarian in Germany. In France and Sweden, the herd journals of treatments were used. Interviews with the farmers were also used in France to double check and complete the data provided by the herd journals of treatments. Antimicrobial usage was then quantified using the ABcheck.UGent™ online tool (http://www.abcheck.ugent.be/) which calculates for each herd and age group the 'treatment incidence' (TI) that represents the number of animals per 1000 receiving a daily dose of an antimicrobial on the farm or the percentage of their life expectancy they are treated with one daily dose of antimicrobials (Timmerman et al., 2006). The TI was calculated using harmonized Defined Daily Doses Animal (DDDA) according to Postma et al. (2015) and harmonized weights at treatment estimated to be 2, 7 and 35 Kg for suckling piglets, weaners and finishers, respectively. The TI of suckling piglets, weaners and finishers were finally combined and standardized to a lifespan of 200 days to correct for possible differences in ages at slaughter between farms. The standardized TI from birth till slaughter is further referred to as TI200d.

Farm characteristics, performance, biosecurity and health status

Farm characteristics (including herd size, number of employees, educational level, experience with pig farming, gender of the farmer, farrowing rhythm and weaning age) were collected using farmer's interviews. Technical performance data included both growing and reproductive performance and were retrieved from the farm management system when available or via farmer's interviews.

Farm biosecurity status was described using the risk-based Biocheck.UGent™ scoring system (http://www.biocheck.ugent.be/); the tool relies on a questionnaire that provides detailed description of farms' practices to prevent pathogens from entering into the farm (i.e. external biosecurity) and to spread within the farm once they entered (i.e. internal biosecurity). It then computes scores between 0 and 100 for sub-categories of external and internal biosecurity, which are subsequently weighted and combined into an internal and external biosecurity score (Laanen et al., 2013). The overall herd biosecurity score is then defined as the average of the internal and external biosecurity scores (Laanen et al., 2013, Postma et al., 2016b).

Additionally, farmers were also asked to indicate on a scale from 1 (= never) to 5 (= every batch) whether they had to treat their pigs because of lameness, gastro-intestinal, respiratory, nervous or cutaneous clinical signs. The information was provided for the year preceding the farm visit and for each age group separately. Vaccination schemes at the time of the visit (i.e. vaccine indication and targeted age group) were also collected.

Selection of the top-farms

In each participating country, a group of top-farms was identified that had both i) high technical performance and ii) low antimicrobial usage. Farms were considered as highly performant when their number of weaned pigs per sow and per year was higher than the national average value, estimated to be 27.7 in Belgium (Cercosoft 2013), 28.7 in France (French Institute for pig and pork industry 2013), 27.0 in Germany (Zentralverband der Deutschen Schweineproduktion 2013) and 23.9 in Sweden (PigWin 2013). Antimicrobial usage was estimated to be low when the farm TI200d was lower than the median TI200d of the country in the study sample (i.e. median TI200d = 107.7, 94.7, 189.0 and 14.3 for Belgium, France, Germany and Sweden, respectively). Farms complying with the two criteria were allocated to the top-farms group and the others to the 'regular' group. As an example, the scatterplot used for selecting the German top-farms is presented in Figure 9. The scatterplots used for selecting the top-farms in the three other countries are available as supplementary material (see Appendix S2). In addition, farms that reported using routine administration of third and fourth generation cephalosporins or fluoroquinolons, considered as critically important antimicrobials (World Health Organization, 2011, World Organisation for Animal Health, 2015), were excluded from the top-farms group and allocated to the regular group. Usage of antimicrobials for growth promotion was not considered here as it is banned in the European Union since 2006 (European Commission, 2003).

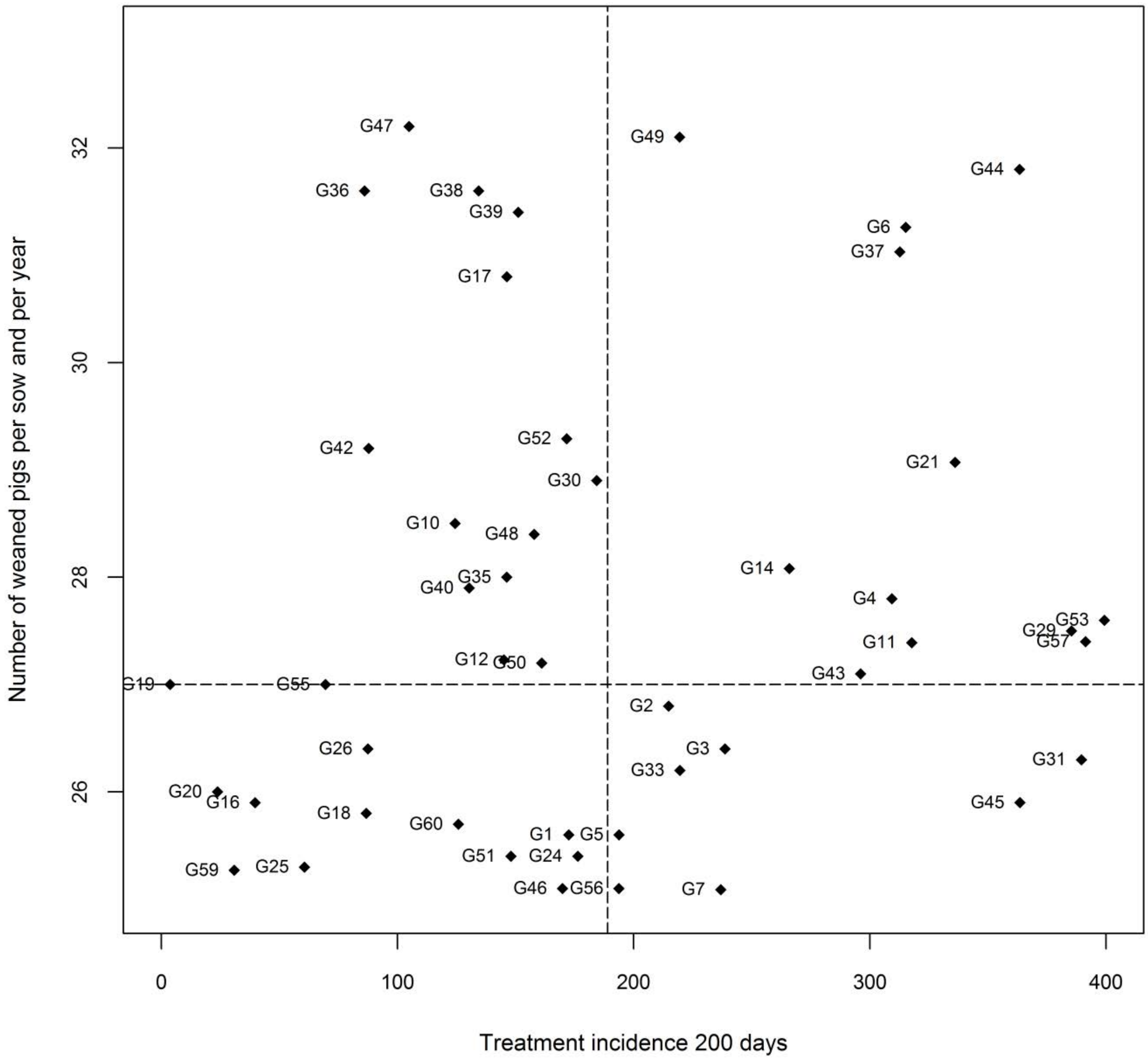

Figure 9. Distribution of the German farms according to their TI200d and their number of weaned pigs per sow and per year

Dotted lines represent the sample median value of the TI200d and the national average of the number of weaned per sow and per year. Farms allocated to the top farms group were those located in the top left quadrant (excluding those located on the quadrant border).

Statistical methods

Two variables were recoded: farrowing rhythm was split into three classes, i.e. 3-week (reference), 1- or 2-week and 4- to 8-week systems. Vaccination scheme against respiratory pathogens ('vac_resp' variable) was defined as a 6-class variable as described in Table 6.

Table 6. Definition of the 6-class variable 'vac_resp' describing the vaccination scheme against respiratory pathogens

	Herd vaccinating against			
vac_resp variable class	*Mycoplasma hyopneumoniae*	Porcine reproductive and respiratory syndrome virus[a]	*Actinobacillus pleuropneumoniae*	Swine Influenza virus
0	no	no	no	no
1	yes	no	no	no
2	yes	no	*A. pleuropneumoniae* OR Influenza virus	
3	yes	yes	no	no
4	yes	yes	*A. pleuropneumoniae* OR Influenza virus	
5	yes	yes	*A. pleuropneumoniae* AND Influenza virus	

[a] Vaccination against Porcine reproductive and respiratory syndrome (PRRS) virus is not allowed in Sweden as Sweden is free from PRRS

Descriptive statistics were used to explore the distribution of farm characteristics between top- and regular farms. Differences were assessed using Wilcoxon rank-sum test and chi-square tests with $P < 0.05$ as a significance threshold. The comparison of top- and regular farms in terms of biosecurity status was first performed using Biocheck.UGent™ scores for overall, internal and external biosecurity, as well as biosecurity sub-categories.

A multivariable logistic regression model was then designed where being in the top- versus regular farms group was the binary dependent variable, and farm characteristics, biosecurity practices and health status were the independent variables. Biosecurity individual practices from the Biocheck.UGent™ questionnaire (rather than biosecurity scores that combine several practices) were retained in the multivariable model to further scrutinize the detailed practices distinguishing top- and regular farms. Univariate logistic regression models were developed and independent variables showing significant associations at $P < 0.25$ were selected for multivariable modelling. The assumption of linearity between outcome and continuous independent variables was checked visually; when linearity assumption was rejected, continuous variables were converted into categorical variables using biologically meaningful cut-offs. In case of multi-collinearity, the most relevant variable was retained in further analysis. Additionally, all biologically plausible two-way interactions were tested. In every model, country of origin was included to control for confounding. A maximal model was first implemented and reduced using a stepwise regression procedure optimizing the Akaike information criterion. Some biosecurity practice variables had missing data (maximum of three missing values per variable); to be able to run the stepwise regression procedure, these were imputed using the mode of the variable in the corresponding country.

Subsequently, a classification tree analysis based on the CART algorithm (Breiman et al., 1984; Loh, 2011) was performed to identify, among farmers located in densely populated pig areas (i.e. with Biocheck.UGent™ score for external biosecurity subcategory 'Environment and region' ≤50), the main predictors for being in the top-farms group. The protocol of Feldesman (2002) was followed; in brief, starting from a single root, a classification tree was built by identifying the variables that split the data (in this case, farms) into subgroups (in this case, top- versus regular farms) with the minimum misclassification rate. For continuous variables, cut-off values were automatically set to minimize the misclassification rate. After each split, data were further divided into strata by nodes defined by the splitting variable. Stratification was continued until the subgroups reached a minimum size as the stop criterion. In the present study, the tree was pruned by setting a minimum number of 15 farms in a node for a split to be attempted and a minimum number of five farms in any terminal node. Considered predictors were similar to those included in the maximal logistic regression model. Ten-fold cross-validation was used to validate the model. Statistical analyses were performed using the open-source environment R V.3.0.2 (R Core Team, 2013, www.r-project.org); the Rpart package was used to implement the classification tree analysis.

4.2.4 Results

Characteristics of the top-farms group

The top-farms group initially consisted of 49 farms. Among them, five farms were routinely administrating third-generation cephalosporins and were excluded from the top-farms group. Thus 44 farms were allocated to the top-farms group including 8 Belgian, 13 French, 13 German and 10 Swedish farms, and 183 farms were allocated to the regular group. Table 7 shows herd characteristics of the top- and regular farms; no difference was observed in herd size, number of employees, education level, number of years of experience, gender of the farmer or distribution of farrowing rhythm systems. Top farms tended to have lower weaning age (P=0.072).

Table 7. Comparison of farm characteristics in the top and regular farms groups

	Regular farms median value (*n* = 183) (95% CI) [a]	Top farms median value (*n* = 44) (95% CI)	P value
Number of present sows (i.e. herd size)	220 (200 ; 250)	216 (171 ; 280)	0.996 [b]
Number of employees per 100 present sows	1.0 (1.0 ; 1.1)	0.9 (0.8 ; 1.2)	0.309 [b]
Highest educational level of the persons in charge of the animals [d]	4 (4 ; 4)	4 (3 ; 4)	0.148 [b]
Number of years of experience of the person mainly responsible for the animals	24 (21 ; 25)	23 (20 ; 25)	0.323 [b]
Proportion of female farmers responsible for the biosecurity in farrowing unit (%)	38.2	29.5	0.286 [c]
Proportion of female farmers responsible for the biosecurity in weaning unit (%)	24.4	13.6	0.125 [c]
Proportion of female farmers responsible for the biosecurity in fattening unit (%)	14.1	6.8	0.194 [c]
Farrowing rhythm			0.635 [c]
3-week system (%)	37.1	29.5	
1- or 2-week system (%)	23.0	25.0	
4- to 8-week system (%)	39.9	45.5	
Weaning age (days)	27.0	23.5	0.072 [b]

[a] 95% Confidence interval
[b] Significance of the 2-sided Wilcoxon Rank-Sum Test
[c] Significance of the Chi-Square test
[d] Education level was measured on a scale from 1= basic (only primary school) to 5= 'university' degree

Biosecurity scores

The biosecurity scores of top- and regular farms are presented in Table 8. Top-farms had significantly higher overall biosecurity scores than regular farms (P=0.011). In particular, they performed better for internal biosecurity (P=0.027), mostly related to the better compartmentalization of the production units and the more appropriate use of equipment (P=0.021). In addition, top-farms tended to have better disease management (e.g. diseased animals were isolated and consistently handled after healthy animals, P=0.082). No difference was observed in the scores obtained for the management of the different production units. Top-farms also tended to have higher external biosecurity (P=0.087); they were located in more favourable environment and region (i.e. with lower pigs density, no manure spread or vehicle transporting pigs from other farms within the area of the farm) (P=0.032) and tended to have better biosecurity practices for personnel and visitors (P=0.086).

Table 8. Comparison of the biosecurity scores between top farms and regular farms

	Regular farms median score (*n* = 183) (95% CI) [a]	Top farms median score (*n* = 44) (95% CI)	P value [b]
Overall biosecurity score	60 (58 ; 62)	65 (60 ; 67)	0.011
Internal biosecurity score	55 (53 ; 57)	58 (54 ; 65)	0.027
Disease management	60 (40 ; 60)	60 (40 ; 80)	0.082
Farrowing and suckling period	50 (50 ; 57)	54 (50 ; 64)	0.196
Nursery unit management	71 (71 ; 71)	71 (64 ; 86)	0.363
Fattening unit management	79 (79 ; 79)	79 (79 ; 79)	0.490
Measures between compartments, and the use of equipment	43 (39 ; 46)	48 (43 ; 54)	0.021
Cleaning and disinfection	45 (45 ; 48)	45 (43 ; 60)	0.185
External biosecurity score	66 (63 ; 67)	66 (63 ; 71)	0.087
Purchase of animals and semen	88 (84 ; 90)	88 (80 ; 88)	0.596
Transport of animals, removal of manure and dead animals	65 (61 ; 70)	65 (61 ; 72)	0.338
Feed, water and equipment supply	40 (30 ; 40)	40 (30 ; 47)	0.331
Personnel and visitors	65 (59 ; 65)	68 (65 ; 71)	0.086
Vermin and bird control	70 (60 ; 80)	70 (60 ; 80)	0.230
Environment and region	60 (50 ; 70)	70 (60 ; 80)	0.032

[a] 95% Confidence interval
[b] Significance of the 1-sided Wilcoxon Rank-Sum Test
Scores were evaluated on a scale from 0 = absence of biosecurity to 100 = perfect biosecurity, using the Biocheck.UGent™ scoring system.

Factors associated with being a top- versus regular farm

Table 9 displays the results of the multivariable logistic regression model. Top-farms were performing better for some biosecurity practices: they had lower chance of having other herds located within a radius of 500 meters (odds ratio (OR) 3.8, 95 per cent confidence interval (95%CI): 1.4; 11.3, P=0.012), and more frequently performed work from younger pigs to older ones (OR 2.4, 95%CI: 1.1; 5.7, P=0.044). Additionally, top-farms had lower occurrence of gastro-intestinal signs in sucklers (OR 2.5, 95%CI: 1.1; 5.6, P=0.026) and lower occurrence of respiratory signs in fatteners (OR 0.6, 95%CI: 0.4; 0.9, P=0.027). Vaccination scheme did not influence significantly the probability of being a top-farm; only farms belonging to the vaccination class 5 (i.e. herds vaccinating against the four selected pathogens) tended to have higher chance of being in the top-farms group. However, the number of herds belonging to this class was relatively limited (n=18 herds).

Table 9. Multivariable logistic regression model for being a top versus regular farm (Belgium, France, Germany, Sweden, 2013-2014)

Variable	% of top farms [a]	Number of herds	Coefficient (se [b])	P value	OR (95%CI [c])
Intercept	19.4	227	-1.20 (1.70)	0.479	-
Carcass storage located in the farm dirty area					
• No	12.3	65	Reference		1.0
• Yes	22.2	162	0.64 (0.49)	0.193	1.9 (0.8 ; 5.2)
Each stable only accessible for visitors from the hygiene lock					
• No	15.4	136	Reference		1.0
• Yes	25.3	91	0.59 (0.39)	0.136	1.8 (0.8 ; 3.9)
Other pig farms located within a radius of 500 meters of the farm					
• Yes	11.4	88	Reference		1.0
• No	24.5	139	1.32 (0.53)	**0.012**	**3.8 (1.4 ; 11.3)**
Work performed from younger pigs to older ones					
• No or not systematically	13.3	90	Reference		1.0
• Yes, systematically	23.4	137	0.86 (0.43)	**0.044**	**2.4 (1.1 ; 5.7)**
Disinfection baths present and used at the entrance of the farm					
• No or not systematically	17.3	185	Reference		1.0
• Yes, systematically	28.6	42	0.94 (0.59)	0.115	2.6 (0.8 ; 8.5)
Occurrence of gastro-intestinal signs in sucklers					
• High (score ≥3)	13.6	103	Reference		1.0
• Low (score <3)	24.2	124	0.90 (0.41)	**0.026**	**2.5 (1.1 ; 5.6)**
Occurrence of respiratory signs in fatteners [e] (score from 1 = never to 5 = every batch)			-0.55 (0.25)	**0.027**	**0.6 (0.4 ; 0.9)**
Vaccination scheme against respiratory pathogens ('vac_resp')					
• Class 0 [d]	13.0	46	Reference		1.0
• Class 1	23.9	46	0.78 (0.61)	0.203	2.2 (0.7 ; 7.6)
• Class 2	30.8	13	0.52 (0.92)	0.570	1.7 (0.3 ; 10.3)
• Class 3	12.5	48	-0.04 (0.78)	0.961	1.0 (0.2 ; 4.7)
• Class 4	23.2	56	0.92 (0.75)	0.215	2.5 (0.6 ; 11.7)
• Class 5	22.2	18	1.80 (1.05)	0.087	6.0 (0.8 ; 50.6)
Weaning age (days) [e]			-0.08 (0.06)	0.184	0.9 (0.8 ; 1.0)
Country					
• Belgium	17.0	47	Reference		1.0
• France	21.7	60	0.38 (0.62)	0.541	1.5 (0.4 ; 5.1)
• Germany	21.7	60	0.27 (0.72)	0.710	1.3 (0.3 ; 5.7)
• Sweden	16.7	60	0.80 (1.09)	0.463	2.2 (0.3 ; 19.5)

P values and OR highlighted in bold are those for which the association is significant (i.e. 95% CI does not contain zero).
[a] Row percentage (i.e. percentage of top farms among all herds in a given class of the independent variable)
[b] Standard error
[c] 95% Confidence interval
[d] Classes of the 'vac_resp' variable are defined in Table 6
[e] Occurrence of respiratory signs in fatteners and weaning age were included in the model as continuous variables

Influential characteristics of a subset of top-farms located in densely populated pig areas

Among 103 farms located in densely populated pig areas (including 25 herds in Belgium, 59 in France, 43 in Germany and 6 in Sweden), 14 belonged to the top-farms group. The classification tree analysis correctly classified 9 out of 14 top farms and 84 out of 89 regular farms. Figure 10 shows that the main predictors for being a top-farm while being located in a densely populated pig area related to internal biosecurity, especially performing work and using equipment in accordance with working lines. Among those farms conducting work in a sequence starting from younger pigs to older age groups, reinforced vaccination against respiratory pathogens was identified as a significant predictor for being a top-farm; however, herds in the vaccination class 3 (i.e. vaccinating against *Mycoplasma hyopneumoniae* and Porcine reproductive and respiratory syndrome (PRRS) virus but not against *Actinobacillus pleuropneumoniae* or Swine Influenza virus) mostly belonged to the regular group. Weaning age <24.5 days was also a predictor for being a top-farm.

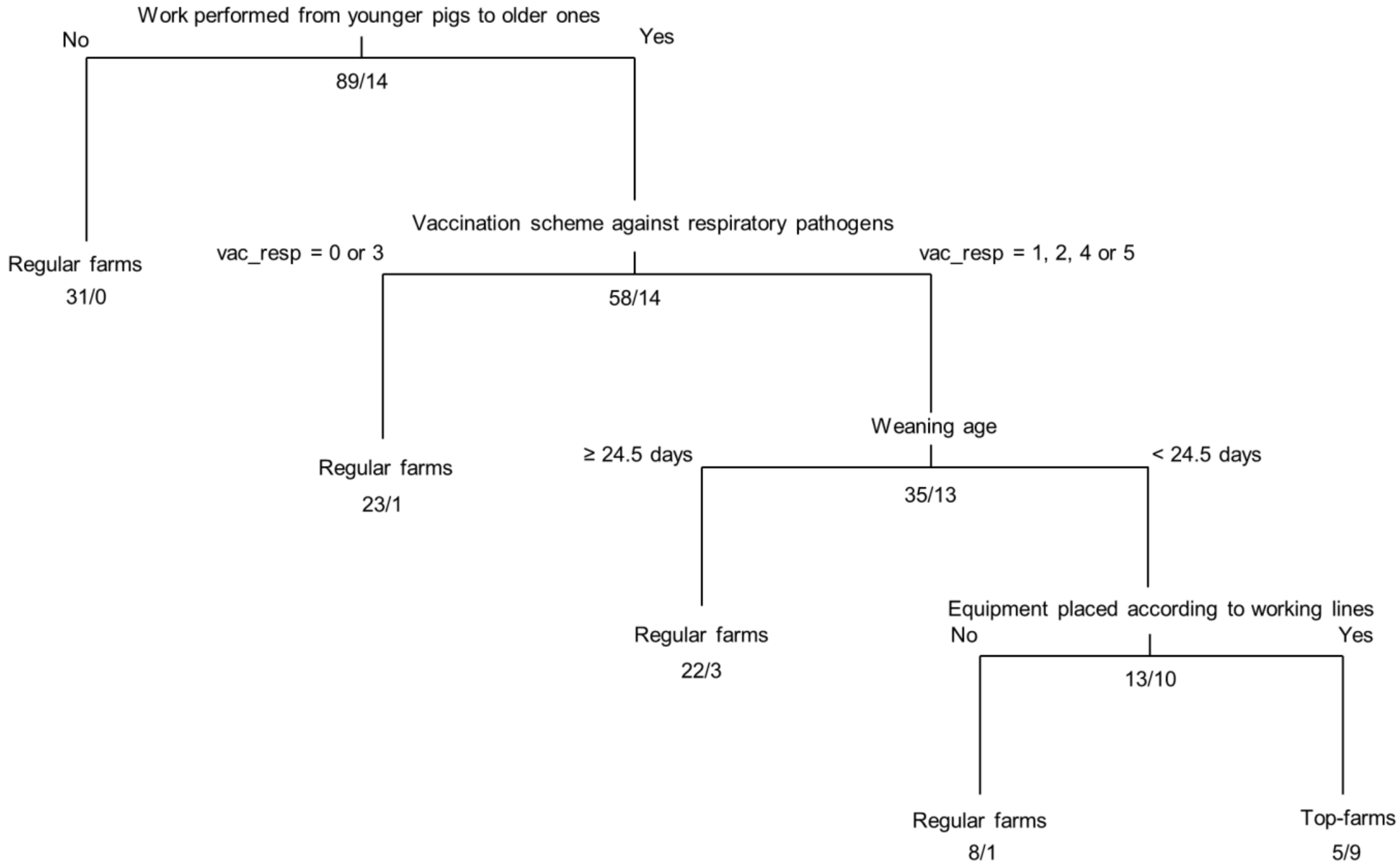

Figure 10. Classification tree identifying the main predictors of being in the top- versus regular farms group if located in densely populated pig areas (Biocheck.UGent™ score for 'Environment and region' ≤50, n=103 herds). The frequency of regular and top-farms (i.e. number of regular farms/number of top-farms) is stated at each intermediate and terminal node. Classes of the 'vac_resp' variable are defined in Table 6. Relative error rate: 0.714. Pooled 10-fold cross-validated error rate (standard deviation): 0.857 (0.233).

4.2.5 Discussion

The aim of this study was to profile farms that had both high performance and low antimicrobial usage across four European countries, which were referred to as 'top-farms'. In order to find characteristics common to top-farms across countries, nationally defined thresholds were used. The number of weaned piglets per sow and per year was selected because of availability of the data, the presence of national reference cut-off values and because this variable has been shown to be positively correlated with the farmers' revenue (Van Til et al., 1991; Galanopoulos et al., 2006). However, it does not provide a good description of the herd performance at the nursery and fattening production stages. Similarly, the TI200d described the amount of antimicrobials administered to growing pigs from birth till slaughter but not to breeding animals. Previous research has shown that antimicrobial usage in growing and breeding pigs are associated (Postma et al., 2016a). In addition, the TI200d provided only a quantitative estimate of the antimicrobial consumption and did not include qualitative attributes such as the antimicrobial class. Therefore, farms administrating routine treatments with third and fourth generation cephalosporins or fluoroquinolons, which are critically important according to WHO (2011) were excluded from the top-farms group.

The profiling showed that top-farms were present in approximately equal proportion across the four countries. Top- and regular farms overall had similar herd characteristics, although top-farms had lower weaning age. Indeed, lower weaning age implies shorter wean-to-service intervals and therefore, higher number of weaned piglets per sow and per year. The lower weaning age in top-farms is likely the result of the used selection criterion (i.e. based on the number of weaned piglets per sow and per year). In a recent study of Postma et al. (2016a), it was shown that weaning age was negatively associated with antimicrobial use (i.e. lower weaning age, higher use). This apparent contradiction might suggest that within the group of farms that have a low weaning age, there are some, identified here as the top-farms, that manage to do this with a limited antimicrobial use whereas for the majority this low weaning age is related to higher antimicrobial use. This is a good illustration of the relevance of identifying this cohort of top-farms that is clearly different from the 'average' farm.

The comparison of Biocheck.UGent™ scores showed that top-farms had higher overall and internal biosecurity, and tended to have higher external biosecurity. In particular, they performed better regarding 'Measures between compartments and the use of equipment' and 'Environment and region'. The multivariable logistic regression model provided further details on associated biosecurity practices and showed, respectively, that top-farms more frequently performed work from younger pigs to older ones and had lower chance of having other herds located within a radius of 500 meters. The latter suggests that top-farms are less exposed to the risk of introduction of pathogens from the farm neighbourhood (Rose and Madec 2002, Nathues et al., 2014).

Top-farms also had fewer gastro-intestinal signs in sucklers and respiratory signs in fatteners. Although herds were visited by the investigators, clinical signs data were reported by the farmer and this could have introduced some information bias. However, the results seem consistent with the hypothesis that pigs from top-farms exhibit fewer clinical signs and therefore, have a reduced need for antimicrobial treatments. Indeed, previous studies have shown that respiratory disorders in fatteners and digestive disorders in piglets are major indications for antimicrobial usage in pig production (Chauvin et al., 2002; van Rennings et al., 2015). Gastro-intestinal signs in weaners are also known to account for an important part of antimicrobial usage, with high amount administered via medicated feed (Callens et al., 2012; Jensen et al., 2012). In the present study however, no difference was observed in the occurrence of gastro-intestinal signs in weaners between top and regular farms (data not shown).

The occurrence of respiratory signs in fatteners and the vaccination scheme against respiratory pathogens were neither correlated nor interacting and were therefore included as two separate independent variables. With the exception of class 5, the vaccination scheme against respiratory pathogens did not significantly influence the probability of being in the top-farms group. This could be related to several aspects: first, vaccination schemes were very different between participating countries. For example, 59 out of 60 Swedish herds belonged to vaccination (i.e. vac_resp) classes 0 and 1; therefore, vaccinating against more respiratory pathogens did not appear as a relevant factor for the Swedish herds to belong to the top-farms group; this is likely the result of the very high pig health status in this country (e.g. Sweden is free of PRRS). A second possible explanation is the fact that the available data only related to the farm vaccination scheme but not to their actual infection status; this made it difficult to distinguish herds not vaccinating because of the absence of the pathogen from herds not vaccinating although the pathogen is present and potentially leads to disease and antimicrobial treatments. Finally it could also be that the expected association between vaccination and antimicrobial use is not that obvious as has also been shown by Postma et al., (2016a), who observed a positive association between number of pathogens vaccinated against and antimicrobial use, suggesting that there are many farms trying to control diseases with a combination of vaccination and antimicrobial use rather than replacing antimicrobial use by vaccines. Future studies are needed to elucidate these associations. Additionally, no difference between vaccination status against *Escherichia coli, Clostridium spp*. and Porcine Circovirus type 2 (PCV-2) were observed between top- and regular farms. The latter is in accordance with Raith et al. (2015) who found a negligible impact of PCV-2 vaccination on total antimicrobial drug use in farrow-to-finish farms. Vaccination status against *Escherichia coli, Clostridium spp* and PCV-2 were therefore not retained in the multivariable model.

The multivariable logistic regression model highlighted that top-farms had significantly higher probability of being located in a sparsely populated pig area. However, 14 farms managed to be in the top-farms group although they were located in densely populated pig areas. The classification tree analysis showed that among those herds located in densely populated pig areas, herds with stricter compartmentation of work and reinforced vaccination against respiratory pathogens had higher chance of belonging to the top farms group. This is in accordance with Fertner et al., (2015), who found, using a qualitative approach, very strict implementation of sectioning among 11 Danish weaner producing farms with low antimicrobial usage and high productivity. However, the tree misclassification rate was quite high, especially in the top-farms group; this could relate to the limited number of top-farms that were located in densely populated pig areas, as well as the unbalanced distribution between top- and regular farms. Still, the study results suggest that it is possible to control the impact of infectious diseases on the herd technical performance using other approaches than high antimicrobial usage like high biosecurity and vaccination, even in farms located in densely populated pig areas with increased risk of pathogens introduction or reintroduction. These results could be generalizable to other countries with similar pig production systems.

4.2.6 Conclusions

In comparison with the regular group, top-farms had fewer gastro-intestinal signs in sucklers and respiratory clinical signs in fatteners, which could partly explain their lower use of antimicrobials and better performance. Top-farms also had better biosecurity and were more frequently located in sparsely populated pig areas. However, some farms did manage to be in the top group although they were located in densely populated pig areas; these had higher internal biosecurity and reinforced vaccination. The results of this study suggest that it is possible to control the impact of infectious diseases using other approaches than high antimicrobial usage, such as biosecurity and vaccination.

4.2.7 Acknowledgements

Many thanks to the farmers and veterinarians who contributed to the study. We thank the French Institute for pig and pork industry for providing access to their technical database. This work was supported by EMIDA ERA-net and the RESPICARE grant of the Institut Carnot Santé Animale.

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4.3 Conclusion of the chapter

This chapter investigated the profile of top-farms that managed to have both low antimicrobial usage and high technical performance. The approach was complementary to the one developed in Chapter 3, where drivers for antimicrobial usage only (i.e. without considering farm performance) were explored.

Similarly to the observations made in Chapter 3, the occurrence of clinical signs, and especially respiratory signs in fatteners, significantly influenced the probability of being in the top-farms group. While Chapter 3 mostly emphasized the influence of external biosecurity (especially farm location) on the level of antimicrobial usage, Chapter 4 showed that both external and internal biosecurity levels had a significant influence on the probability of being a top-farm. At the difference of Chapter 3, farm characteristics had little influence of the probability of being a top-farm. Only weaning age was negatively associated with the probability of being a top farm, whereas Chapter 3 had shown that farms with higher weaning age had lower antimicrobial usage. This is because weaning age also influences the farm reproductive performance, especially the number of weaned per sow per year.

These findings could be considered in future mitigation strategies aiming not only to reduce antimicrobial usage, but also to maintain high performance level.

CHAPTER 5: TECHNICAL AND ECONOMIC IMPACT OF THE REDUCTION OF ANTIMICROBIAL USAGE IN PIG PRODUCTION

5.1 Chapter introduction

While Chapters 3 and 4 relied on an observational, cross-sectional study, aiming at exploring the key drivers for antimicrobial usage in pig production, Chapter 5 presents an intervention study conducted as part of the MINAPIG project, in order to assess the potential for reducing antimicrobial usage in pig production and to quantify the associated impact on farm performance. More specifically, herd-specific interventions were implemented in 70 farrow-to-finish pig farms located in Belgium, France, Germany and Sweden, and the following questions were explored: i) how much antimicrobial usage can be reduced at herd level? ii) with what technical and economic impact? iii) with what compliance with the predefined intervention plan?

Loesken et al. (in prep) described in details the observed reduction in antimicrobial usage (question i), including the reduction in treatment incidence per age group, antimicrobial class and administration route. In Chapter 5 of this thesis are addressed the questions ii) and iii).

Additionally, the results of the intervention study conducted in France were presented at the 48th Journées de la Recherche Porcine organized in Paris, France, on February 3-4th 2016. Every farmer and herd veterinarian who participated in the study conducted in France also received an individual feedback report of the study conducted at their farm. An example of such a report is provided in Appendix S3.

5.2 Publication

Herd-level technical and economic impact of reducing AM usage in pig production: key outcomes of a multi-country intervention study

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5.2.1 Abstract

Because of the rising threat from antimicrobial resistance, pig farmers are strongly encouraged to reduce their antimicrobial usage. In order to achieve national and European reduction targets, herd level action is needed. Alternative, especially preventive measures have to be implemented to reduce the need for antimicrobial treatments. However, little is known about the feasibility, effectiveness and return on investment of these measures. The objective of this study was to assess, across four countries, the technical and economic impact of herd-specific interventions aiming at reducing antimicrobial usage in pig production while implementing alternative measures.

An intervention study was conducted between February 2014 and August 2015 among 70 farrow-to-finish pig farms located in Belgium, France, Germany and Sweden. Herd-specific interventions were defined together with the farmer and the herd veterinarian. Farms were followed up over one year and their antimicrobial usage and technical performance were compared with those from the year before intervention. Compliance with the intervention plan was also monitored. Changes in margin over feed cost and net farm profit were estimated in a subset of 33 Belgian and French farms with sufficient data, using deterministic and stochastic modelling.

Following interventions, a substantial reduction in antimicrobial use was achieved, without impacting the overall farm technical performance. A median reduction of 47.0% of antimicrobial usage was obtained across four countries when expressed in terms of treatment incidence from birth to slaughter, corresponding to a 30.5% median reduction of antimicrobial expenditures. Farm compliance with the intervention plans was high (median: 93%; min-max: 20-100) and farms with higher compliance tended to achieve bigger reduction (ρ= -0.18, p= 0.162). No association was found between achieved reduction and type or number of alternative measures implemented. Mortality in suckling piglets, weaners and fatteners, daily weight gain and feed conversion ratio did not significantly change over the course of the study, whereas the number of weaned per sow per year slightly increased (from 27.2 to 27.4; p= 0.008). The median change in the net farm profit among Belgian and French farms was estimated to be €4.46 (Q25-Q75:-32.54; 80.50) and €1.23 (Q25-Q75:-31.12; 74.45) per sow per year using the deterministic and stochastic models, respectively. It was more influenced by the change in the feed conversion ratio and daily weight gain than by the change in antimicrobial expenditures or direct net cost of the intervention. Therefore, costs of alternative measures should not be perceived as a barrier, as long as they contribute to maintain or improve growth performance.

Key words: Antibiotics, preventive measures, compliance, technical performance, margin over feed cost, farm net profit

5.2.2 Introduction

Because of the increasing concern about antimicrobial resistance, livestock farmers are strongly encouraged to reduce their antimicrobial usage (WHO, 2015). The prudent use of antimicrobials in veterinary medicine is a core pillar of the European Union (EU) action plan against the rising threat from antimicrobial resistance (European Commission, 2011). For example, following the discovery of the mcr-1 resistance gene in China in 2015 (Liu et al., 2016), EU member states were asked to reduce their use of colistin in animals up to a level of 5 mg per population correction unit within 3 to 4 years; this represents a 65% reduction across all EU countries when compared with the level used in 2016 (European Medicines Agency, 2016). Colistin is one of the most commonly used antimicrobials to prevent gastro-intestinal disorders in piglets after weaning, and contributes to a large part of antimicrobial usage in pig production (Sjölund et al., 2016).

In order to successfully reduce antimicrobial use at national and European levels, on farm action is needed. The implementation of alternative, mostly preventive, measures has been proposed as a way to further reduce the need for antimicrobials on farms (European Commission, 2011). However, little is known about the feasibility, effectiveness and return on investment of these alternatives. Reducing antimicrobial usage can be perceived as being risky by stakeholders in the field; this is because it does not only imply direct costs (e.g. to implement a new vaccination), but might also come with indirect costs, e.g. increased mortality or reduced growth performance. Pig farmers were shown to have high concerns about the financial situation at their farm (Visschers et al., 2015). Although other drivers (e.g. social drivers) do exist, economic drivers are known to strongly influence farmers' choices, including choices related to antimicrobial treatment practices (Coyne et al., 2014; Garforth, 2015). Risk avoidance and economic considerations were also mentioned as strongly influencing antimicrobial prescribing practices among veterinarians (Speksnijder et al., 2015).

An expert opinion elicitation survey conducted among 111 European pig experts identified reinforced internal and external biosecurity as well as improved housing conditions (e.g. climate of the stable) as the most promising alternatives in terms of perceived effectiveness, feasibility and return on investment (Postma et al., 2015a). A recent intervention study conducted among 61 Belgian pig farms showed that a 52% reduction of antimicrobial usage from birth till slaughter, when expressed in terms of treatment incidence, could be achieved without impairing the herd production performance (Postma et al., 2016a); the average enterprise profit was estimated to increase by 42.99 € (CI 95% -79.13; 151.43) per sow per year following the implementation of the interventions (Rojo-Gimeno et al., 2016). The results from Rojo-Gimeno et al. (2016) showed high variability, and it is unknown whether these results can be generalized to other contexts, e.g. other countries or other types of alternatives. Moreover, no attempt was made to explore the association between achieved antimicrobial usage reduction and compliance, type or direct costs of implemented measures.

Therefore, the objective of this study was to assess, across four countries, the technical and economic impact of herd-specific interventions aiming at reducing antimicrobial usage in pig production while implementing alternative measures. More specifically, we aimed to explore the following questions: i) how much antimicrobial usage can be reduced at herd level, ii) with what impact on the technical performances and net farm profit and iii) with what compliance with the predefined intervention plan.

This study was conducted as part of the MINAPIG Emida Era-Net project that aimed to evaluate strategies for raising pigs with minimal antimicrobial usage.

5.2.3 Material and methods

An intervention study was conducted between February 2014 and August 2015 among 70 farrow-to-finish pig farms located in Belgium (n=16), France (n=20), Germany (n=25) and Sweden (n=9). Figure 11 provides a summary of the study workflow and supports the description of the method.

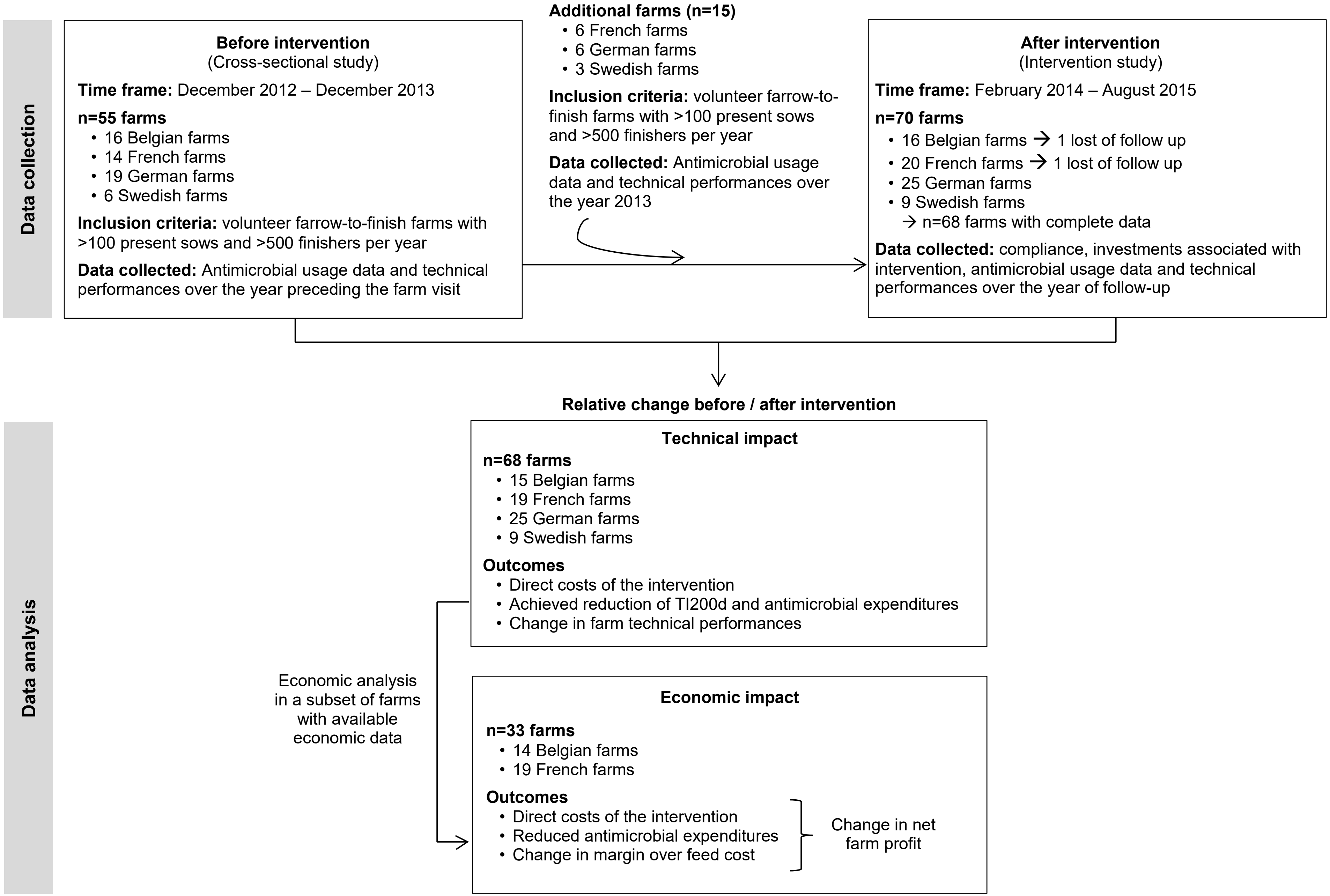

Figure 11. Summary of the study workflow

Recruitment of participating farms

Farms were primarily recruited among those that previously participated, between December 2012 and December 2013, in a cross-sectional study that aimed to document antimicrobial use and to explore risk factors for antimicrobial usage in pig production related with the farm management characteristics, biosecurity practices and health status, as well as the farmer's attitude and behavior towards antimicrobial usage (Postma et al., 2016b; Sjölund et al., 2016; Visschers et al., 2016). The cross-sectional study had been conducted on a convenience sample of 227 farrow-to-finish pig farms (47 in Belgium and 60 in France, Germany and Sweden) with more than 70 present sows and more than 500 finishers produced annually. More details on herd selection are provided in Sjölund et al. (2016).

In Belgium, of the 47 herds participating in the cross-sectional study, 29 were asked about their interest in participation in the intervention study. Of these 29 herds, 16 agreed on participation. The 13 herds that were not willing to participate refused due to a combination of lack of time and/or concerns about possible consequences for the herds health status (n=8), or had extended animal health problems on the farm at the start of the project (n=1). The 18 herds that were not selected by the researchers had already very low antimicrobial usage (n=3), smaller numbers of sows (n=3), had a lack of time due to personal or business related problems (n=3), stopped sow practice in the meantime (n=1) and eight already made clear not to be interested in participating in a follow-up study during the cross-sectional study.

In France, the 30 farms (i.e. 50% of the farms enrolled in the cross-sectional study) with the highest antimicrobial use were selected as potential candidates for enrollment in the intervention study. Herd veterinarians were first contacted and asked about their interest in participating in the intervention study together with the pre-identified farmer. In case of acceptance, herd veterinarians contacted the farmer to ask if they were interested in participating. Five veterinarians (in charge of six herds) did not respond after several attempts to contact them and one veterinarian (in charge of three herds) refused to participate. One veterinarian felt it was not possible to cooperate with the identified farmer. Six farmers refused to participate because of lack of time, lack of interest or because of concerns about the potential consequences from such an intervention on the health status of their pigs. Therefore, 14 French farms previously involved in the cross-sectional study were enrolled in the intervention study. Six additional farms were recruited based on the herd veterinarian's and farmer's willingness to participate. These farms complied with the same selection criteria as those used in the cross-sectional study.

In Germany, farmers who participated in the cross-sectional study were invited, during the cross-sectional study visit, to take part to the intervention study; 19 farmers accepted. Six additional farmers were recruited by contacting a veterinarian practice that provided contacts from interested farmers. Therefore, 25 German herds were enrolled in the intervention study.

In Sweden, all farmers participating in the cross-sectional study were informed about the planned prospective study during the farm visit of the cross-sectional study to give them the opportunity to participate. Six herds enrolled in the cross-sectional study agreed to enroll in this study. An additional three herds fulfilling the inclusion criteria of being a farrow-to-finish herd with ≥70 sows and producing ≥ 500 fatteners were enrolled. These three herds were recruited with the aid of herd veterinarians from the Farm & Animal Health organization (G&D) (formerly Swedish Animal Health Service). The herd veterinarians had all received training for data collection for the cross-sectional study as previously described (Sjölund et al., 2015; Sjölund et al., 2016).

In Belgium and France, farmers and veterinarians did not receive financial compensation for participating in the intervention study, whereas in Germany and Sweden, farmers received €200 and €1300, respectively, to compensate the time devoted to data collection.

Definition of the herd intervention plan

In each herd, an initial farm visit was organized in order to define a herd-specific intervention plan aiming at implementing preventive measures to reduce the level of antimicrobial usage of the farm. In Belgium, France and Germany, the initial visit was organized together with the farmer, the herd veterinarian, the herd advisor (when available) and the MINAPIG researcher, whereas in Sweden, either the herd veterinarian or one of two MINAPIG researchers or the responsible herd veterinarian from G&D participated in the initial visit with the farmer. When available, observations from the cross-sectional study including a detailed description of the farm antimicrobial usage, management and biosecurity practices as well as the health status of the pigs, were used as a basis for discussion. A wide range of possible alternatives to antimicrobials was considered (Postma et al., 2015a); these related to six main categories of measures, namely: i) improvement of external biosecurity status, ii) improvement of internal biosecurity status, iii) modifications of the herd vaccination scheme, iv) changes in feed or drinking water composition, safety or quality, v) better pig health care or welfare and vi) pig stable climate and other zootechnical measures.

Alternatives considered by the farmer and the veterinarian as being both feasible and the most promising in regards of the herd health problems were selected for the intervention plan. Country-specific legislation, e.g. in relation to the authorization of the therapeutic use of zinc oxide as feed additive, was also considered to select possible alternative measures. In Belgium, France and Germany, selected alternatives were consigned on a form the farmer and herd veterinarian had to sign to confirm they agreed to implement the defined plan from a certain date. In Sweden, farmers signed a contract to ensure they would participate and receive financial compensation if they delivered complete data. Therefore, each herd was implementing a different intervention plan, both in terms of the number and types of measures implemented. It was expected that using tailor-made interventions would improve the farmer's compliance with the predefined plan and more effectively improve health thereby reducing the need for antimicrobial treatments.

Follow-up of the intervention

Interventions were monitored over one year following the beginning of the intervention; the follow-up included a minimum of two farm visits (i.e. one intermediate and one final visit) and a maximum of six farm visits, as well as intermediate phone calls with the farmer and the herd veterinarian. Collected data included both annual data from the entire year of follow-up, as well as data specifically targeting three batches of pigs produced at equal intervals during the year of follow-up; the latter aimed at facilitating the prospective collection of data not necessarily collected in routine by the farmer and therefore, hardly available retrospectively (e.g. growth performance and mortality data). Collected data were entered by the MINAPIG researchers into a common Microsoft Office Access© (version 2010) database in order to improve data quality and harmonization, and therefore facilitate further data analysis.

At each follow-up visit, farmers had to report on a scale from 1 (=no attempt to implement the measure) to 5 (=perfect implementation), whether each predefined measure was implemented or not. Reasons for non-compliance were explored in order to identify possible solutions when available. Herd veterinarians and MINAPIG researchers were also asked to comment on the observed compliance; as high agreement was generally obtained with the score reported by the farmer, no adjustment of reported scores was considered necessary. An average compliance score over the year of follow-up was computed for each predefined measure and combined into a farm percentage of compliance with the intervention plan as initially defined.

Technical impact of the intervention

Quantification of the direct net cost of the interventions

Farmers were asked to provide an estimate of the investments associated with the intervention implemented at their farm. These included four components: i) the purchase of equipment (e.g. water pump) or single expenses (e.g. diagnostic testing only performed once); ii) the purchase of consumables (e.g. vaccine doses or disposable overalls), iii) the extra workload associated with the proposed measures and iv) the visits of the herd veterinarian or other external stakeholder (e.g. stable climate expert) intervening as part of the intervention study. Farmers also had to report whether they stopped any other activity following the implementation of the intervention (e.g. some farms stopped vaccinating against a certain disease to start vaccinating against another disease); in case they had, associated costs were subtracted from the costs of the intervention.

Subsequently, a cost accounting analysis was performed to quantify the cost associated with each component of the investments made as part of the intervention, and therefore estimate the direct net cost of the intervention:

Direct net cost of the intervention (€ per sow per year) = Costs of equipment or single expenses (€ per sow per year) + Costs of consumables (€ per sow per year) + Costs of extra workload (€ per sow per year) + Costs of veterinarian or other stakeholder visits (€ per sow per year) (1)

Costs associated with the purchase of equipment, consumables or single expenses were estimated by multiplying the number of units purchased in a year by the unit price, the latter being either provided by the farmer or defined using prices found in the literature (see Appendix 1). Linear depreciation was applied in case purchased equipment was likely to be used over several years, e.g. a new quarantine building (see Appendix S4 for an estimate of the equipment expected lifespan). The costs of extra workload was estimated by multiplying the annual number of hours devoted to the intervention by a standard rate estimated to be €9.61 per hour (i.e. the minimum gross wage in France on January 1st 2015); distinction was made between the initial (e.g. setting up a vaccination scheme) and routine (e.g. vaccinating every batch) workload associated with the intervention. A cost was put on the visits of the herd veterinarian or other external stakeholder by multiplying the number of hours they spent on assisting the farmer as part of the intervention with a standard wage estimated to be €100 euros per hour for veterinarians and €70 per hour for other stakeholders; these wages were derived from those typically used for herd visits in the cattle sector in France. In reality, pig farmers usually have a yearly contract with a herd veterinarian or technician and do not pay for every individual visit. However, it was felt the extra support from these stakeholders should also be considered as part of the costs associated with the intervention. The costs of the visits made by the MINAPIG researchers were not included in the cost accounting analysis.

Quantification of the achieved antimicrobial reduction

In agreement with the farmer, the herd veterinarian of Belgian, French and German participating farms was asked to provide detailed receipts of all antimicrobial expenditures of the farm during the year of follow-up. In Sweden, antimicrobial use data were retrieved from the herd treatment records, as previously described by Sjölund et al. (2015). Antimicrobial use data included commercial products names, number and size of antimicrobial packages. During the follow-up discussions, farmers were asked to re-allocate the purchased antimicrobials to a given animal category (i.e. suckling pigs, weaners and fatteners). Additionally, herd demographics data were retrieved from the farm management system and included the average number of present sows and the number of suckling pigs, weaners and fatteners produced during the year of follow-up of the intervention. These were used to estimate the population at risk of being treated with antimicrobials. Antimicrobial usage data were then converted into an indicator called 'treatment incidence' (TI) that represents the number of animals per 1000 receiving a daily dose of an antimicrobial on the farm or the percentage of their life expectancy they are treated with one daily dose of antimicrobials (Timmerman et al., 2006). The TI was calculated using harmonized Defined Daily Doses Animal (DDDA) as described by Postma et al. (2015b) and harmonized weights at treatment estimated to be 2, 7 and 35 kg for suckling pigs, weaners and finishers, respectively. The TI of suckling pigs, weaners and finishers were combined and standardized to a lifespan of 200 days to correct for possible differences in ages at slaughter between farms (see Sjölund et al. (2016) for calculation details). The standardized TI from birth till slaughter is further referred to as TI200d.

Additionally, a cost was put on the herd annual antimicrobial expenditures. This was obtained by multiplying, for each administration route and active substance, the total amount of active substance purchased over the year of follow-up by a standard unit price (in € per gram of active substance); the latter was estimated from the average price across commercial products, product compositions (i.e. amount of active substance per amount of product) and package sizes as used by the two main retailers of veterinary antimicrobial products in France. MINAPIG Consortium partners reviewed the initial list and provided input on combinations of administration route/active substance not authorized in France. Antimicrobial prices from a previous study conducted in Belgium were also used to check for major discrepancies between Belgian and French prices (Rojo-Gimeno et al., 2016). Additionally, a French pig veterinary practitioner was invited to review the initial list of prices and suggested minor changes that were included in the consolidated list of prices (see Appendix S5).

For each participating herd, the TI200d and antimicrobial expenditures over the intervention year were compared with those observed in the same herds during the cross-sectional study; details on how these data were collected were presented by Sjölund et al. (2016). In brief, the cross-sectional survey collected data from antimicrobial expenditures, treatment records and deliveries during the year preceding the farm visits; the visits were conducted between December 2012 and December 2013. For the 15 farms that had not participated in the cross-sectional study, as well as the 14 French farms that had participated but for which antimicrobial usage data were only available for the last batch produced before the visit, antimicrobial expenditures or treatment records for the year

2013 were collected at the first visit of the intervention study in order to reflect the herd level of antimicrobial usage before intervention (see Figure 11).

Change in farm technical performance

Additionally, data on the average farm technical performance over the year of intervention were collected at the final visit of follow-up, using input either from the farm management system, when available, or directly from the farmer. These included both reproductive performance (i.e. litter size and farrowing index) and growth performance (i.e. feed conversion ratio and daily weight gain during the fattening period, final weight of the finisher pigs), as well as mortality rates in suckling pigs, weaners and fatteners. Average farm technical performance over the year of intervention was then compared to farm technical performance collected in the same farms during the cross-sectional study; the latter were average technical performance data over a one-year period preceding the farm visit (Postma et al., 2016b). For the 15 farms that had not participated in the cross-sectional study, technical performance during the year 2013 was collected at the first visit of the intervention study (see Figure 11).

Statistical analysis

Kruskal-Wallis rank sum test was performed to test for differences in median compliance score between categories of measures. Spearman rank correlations were used to explore the associations between the farm level of compliance and the number of measures or the achieved TI200d reduction, as well as the association between the direct net cost of the intervention and the achieved TI200d reduction. Paired sample Wilcoxon testing was performed to compare TI200d, antimicrobial expenditures and farm technical performance before and after intervention. Normal distribution of variation in net farm profit was assessed using Shapiro-Wilk normality testing. A p-value of 0.05 was used as a significance threshold. Descriptive and analytical statistics were performed using the open-source environment R 3.0.2 (R Core Team, 2013, www.r-project.org).

Economic impact of the intervention

The herd-level economic impact of the interventions was estimated following a two-step approach. First, the economic impact of the observed changes in farm technical parameters was estimated by calculating the change in margin over feed cost. Second, the change in margin over feed cost was combined together with the direct net costs of the intervention and the change in antimicrobial expenditures to estimate the change in net farm profit associated with the intervention (see Figure 11).

Change in margin over feed cost

In a first step, the economic impact of observed changes in farm technical parameters was estimated by calculating the change in margin over feed cost. The farm margin over feed cost is defined as (Barnard and Nix, 1979):

Margin over feed cost = Revenues – Feed costs (2)

with revenues arising either from the sale of marketable finisher pigs, or from the sale of piglets:

Revenues (€) = Amount of finishers produced (kg live weight) x Finisher price (€ per kg live weight) + Number of piglets sold x Piglet price (€ per piglet) (3)

and feed costs arising from the feed consumed by sows, piglets and finishers, as described in Eq. (4):

Feed costs (€) = Amount of feed consumed by sows (kg) x Sows feed price (€ per kg feed) + Amount of feed consumed by piglets (kg) x Piglets feed price (€ per kg feed) + Amount of feed consumed by finishers (kg) x Finishers feed price (€ per kg feed) (4)

Therefore, the outcome of this step was an estimation of the change in the margin over feed cost before and after intervention:

Δ Margin over feed cost$_{after\text{-}before}$ (€ per sow per year) = Δ Revenues$_{after\text{-}before}$ (€ per sow per year) – Δ Feed costs$_{after\text{-}before}$ (€ per sow per year)) (5)

Change in net farm profit

In a second step, the initially obtained Δ Margin over feed cost$_{after\text{-}before}$, that related to changes in the farm technical parameters only, was expanded to include the costs associated with the intervention. To that end, the change in the net farm profit was calculated as the difference between the Δ Margin over feed cost$_{after\text{-}before}$ and the intervention costs; the latter included both variable and fixed costs:

Δ Net farm profit $_{after\text{-}before}$ (€ per sow per year) = Δ Margin over feed cost$_{after\text{-}before}$ (€ per sow per year) - Δ Variable costs intervention$_{after\text{-}before}$ (€ per sow per year) – Δ Fixed costs intervention$_{after\text{-}before}$ (€ per sow per year) (6)

The change in variable costs other than those associated with the intervention or feed was considered to be zero. Similarly, the change in fixed costs other than those associated with the intervention was considered to be zero.
Combining Eq. (1) and Eq. (6), the variation in the net farm profit could be expressed as:

Δ Net farm profit $_{after\text{-}before}$ (€ per sow per year) = Δ Margin over feed cost$_{after\text{-}before}$ (€ per sow per year) - Δ Antimicrobial expenditures $_{after\text{-}before}$ (€ per sow per year) – Direct net cost of the intervention (€ per sow per year) (7)

Both the feed conversion ratio and daily weight gain during the fattening period strongly influenced the margin over feed cost. Because German and Swedish farms had no data for these parameters, the estimation of the change in margin over feed cost was only performed for the Belgian (n=14) and French farms (n=19 farms) (see Figure 11). However, the feed conversion ratio and daily weight gain were missing in five and four Belgian farms, respectively, and in two French farms. For those farms, feed conversion ratio and daily weight gain were assumed to be equal before and after intervention.

Implementation in the Pig2win model

The changes in margin over feed cost and net farm profit were estimated using an existing input-output production economic model called 'Pigs2win' that was developed in Microsoft Excel© (Van Meensel et al., 2012). The details of the model were presented by Rojo-Gimeno et al. (2016) and a simple version of the model is freely accessible online (www.remiweb.be, in Dutch). To be able to calculate a margin over feed cost and net farm profit, the Pigs2win model requires 41 input parameters to be informed, of which 19 parameters are related to the post-weaning and fattening periods and 22 parameters to the farrowing period (see Appendix S6). Because of privacy and practical reasons, some of these parameters were not available from the farms enrolled in the intervention study. Therefore, reference farms, i.e. virtual farms representing a typical farrow-to-finish pig farm were created, and the change of margin over feed cost and net farm profit of participating farms were estimated by simulating the effect that the observed changes in farm technical parameters would have had on the margin over feed cost and net farm profit of the reference farms, assuming they implemented similar interventions.

Reference farms were generated separately for Belgium and France. In Belgium, efficiency analysis was used to generate 11 virtual farrow-to-finish pig farms out of the Farm Accountancy Data Network (FADN) dataset that monitored farrow-to-finish farms in Flanders from 2010 to 2012 (Rojo-Gimeno et al., 2016). Input parameters of the 11 virtual farms were then averaged to obtain only one reference farm which allow comparability with the French data. The French reference farm was defined using input from the French Pork and Pig Institute (IFIP, 2014) and the Agriculture and Horticulture Development Board (InterPIG) (AHDB, 2016). Detailed description of the Belgian and French reference farms is available in Appendix S6.

Pig and feed prices were defined identically before and after intervention so that the observed changes in margin over feed cost could be attributed to the changes in the farm technical performance only. A deterministic model was first developed using average pig and feed prices over a three-year period in Belgium and France. In order to account for the volatility of pig and feed prices, stochastic distributions were then attributed to pig and feed prices using @Risk 7.0 (Palisade Corporation, Ithaca, NY, US) (see Table 10). Because feed and pig prices in piglets, sows and finishers show similar trends over time, a Pearson correlation coefficients matrix was inserted in the model, as described in Rojo-Gimeno et al. (2016), to ensure randomly selected pig and feed prices were correlated (see Appendix S7). Latin Hypercube sampling was used with a fixed seeder of 1 to ensure all simulations provided repeatable results. The stochastic input-output production economic model was simulated for 1,000 iterations. A scenario based on a fixed number of sows was used in case of overstocking, whereas a variable number of sows was used in the absence of overstocking (van Meensel and Lauwers, 2010).

Table 10. Feed and pig prices input parameters used in the input-output production economic model

	Belgium			France		
	Deterministic	Stochastic	Source	Deterministic	Stochastic	Source
Feed for piglets (€ per kg)	0.32	BetaPert (0.25; 0.32; 0.39)	Flemish Department of Agriculture and Fisheries, 2012	0.13	BetaPert (0.11; 0.12; 0.13)	French National Institute of Statistics and Economic Studies, 2016
Feed for finishers(€ per kg)	0.26	BetaPert (0.19; 0.26; 0.33)	Flemish Department of Agriculture and Fisheries, 2012	0.23	BetaPert (0.23; 0.26; 0.31)	French National Institute of Statistics and Economic Studies, 2016
Feed for sows(€ per kg)	0.27	BetaPert (0.21; 0.27; 0.33)	Flemish Department of Agriculture and Fisheries, 2012	0.12	BetaPert (0.12; 0.13; 0.15)	French National Institute of Statistics and Economic Studies, 2016
Finishers (€ per kg)	1.05	BetaPert (0.88; 1.05; 1.35)	Vanden Avenne 2012	1.48	BetaPert (1.18; 1.48; 1.86)	FranceAgriMer 2016
Piglets (€ per piglet)	27.45	BetaPert (20.00; 27.45; 36.75)	Vanden Avenne 2012	40.26	BetaPert (29.40; 40.26; 51.75)	FranceAgriMer 2016

Sensitivity analysis

Subsequently, a sensitivity analysis was performed to identify the input parameters that mostly influenced the change in net farm profit. To that end, distributions were fitted to the data on farm technical parameters, change in antimicrobial expenditures and direct net cost of intervention, using input from Belgian and French participating herds. Distributions were fitted with @Risk 7.0 (Palisade, Ithaca, NY) and selected to minimize the Akaike information criterion. Detailed information on the fitted distributions for each of the explored parameters can be found in Appendix S8. Sensitivity analyses were performed separately for Belgium and France as the models were parameterized differently.

Additionally, a break-even analysis was conducted in order to explore what change in overall antimicrobial prices and in finisher price would allow for 90% of the Belgian and French participating farms to have a Δ Net farm profit $_{\text{after-before}}$ ≥0, assuming all other model parameters, including the demand for antimicrobials and pork products, remain equal.

5.2.4 Results

Description of interventions

Out of the 70 farms that entered the intervention study, two were lost of follow-up and excluded from further analysis because of farmer's personal issues (n=1) or because of a change, in the course of the study, of the herd veterinarian to another veterinarian who was not willing to participate (n=1). Therefore, 68 farms participated in the study, including 15 farms form Belgium, 19 from France, 25 from Germany and 9 from Sweden (Figure 11). Table 11 provides an overview of the measures included in the intervention plans, as well as their compliance per category of measures. Feed- and water-related measures were the most common, especially those related to the use of zinc oxide in piglets. Eleven Belgian herds implemented therapeutic use of zinc oxid administered via feed at 2500 ppm during 10 to 14 days post-weaning; indeed, a recent change in the Belgian legislation authorized this practice in September 2013, shortly before the beginning of the intervention study (AMCRA, 2013). Seven German herds switched from using a combination of colistin and zinc oxid in feed to zinc oxide only, administered at 150 ppm during 7 to 14 days around weaning. Vaccination, as well as improvement of pig health care or welfare, was also commonly implemented. The median number of measures implemented in a farm was 2 (min: 1; max: 13). Farm compliance with the predefined intervention plan was generally high (median: 93%; min: 20%; max: 100%) and negatively correlated with the number of measures included in the intervention plan (Spearman's rank correlation $\rho=-0.33$, $p<0.01$). Compliance tended to be lower with biosecurity-related measures than for measures of other categories, although the difference was not statisticaly significant (Kruskal-Wallis chi-squared=6.02, p-value=0.304).

Table 11. Distribution of implemented measures and their compliance (n=68 farrow-to-finish pig farms)

Type of measure included in the intervention plan (n=number of farms that included the measure in their plan)	Median compliance percentage (min; max)
Improvement of external biosecurity status (n=9)	73 (20; 100)
Purchasing policy / gilts acclimatization (n=8)	
Removing of animal carcasses (n=2)	
Vermin control (n=1)	
Improvement of internal biosecurity status (n=20)	75 (0; 100)
Suckling period management (care of piglets) (n=9)	
Farm compartmentalizing, working lines (n=6)	
Reinforced cleaning and disinfection (n=6)	
Modifications of the herd vaccination scheme (n=30)	88 (0; 100)
Implementation of a new vaccination (n=29)	
Porcine Circovirus 2 (n=5)	
Porcine reproductive and respiratory syndrome virus (n=4)	
Actinobacillus pleuropneumoniae (n=4)	
Shiga toxin-producing *E. coli* (n=4)	
Lawsonia intracellularis (n=4)	
Clostridium spp (n=3)	
Atrophic rhinitis (n=2)	
Haemophilus parasuis (n=2)	
Influenza virus (n=1)	
Mycoplasma hyopneumoniae (n=1)	
Escherichia coli (n=1)	
Other vaccinations [a] (n=5)	
Change of existing vaccination protocols (n=5)	
Changes in feed or drinking water composition, safety or quality (n=45)	87 (0; 100)
Zinc oxide (n=18)	
Feed scheme revision (n=10)	
Water acidification (n=8)	
Cleaning and disinfection of water pipes (n=7)	
Phytotherapy (n=7)	
Other feed additives [b] (n=7)	
Feed quality improvement (e.g. change in fat, protein or fiber content) (n=5)	
Feed acidification (n=4)	
Pre- and pro-biotics (n=4)	
Water quality control (n=3)	
Better pig health care or welfare (n=21)	89 (0; 100)
Increased diagnostics (n=7)	
Alternative treatments protocols in case of symptoms (e.g. with anti-inflammatory products or prostaglandins) (n=5)	
Revision of deworming scheme (n=4)	
Stopped castration (n=3)	
Hospital pens put in place (n=3)	
Strict euthanasia of runt suckling piglets(n=1)	
Pig stable climate and other zootechnical measures (n=14)	100 (20; 100)
Climate adjustments (n=7)	
Animal transfer adjusted to avoid re-mixing of piglets remixing or having pens with heterogeneous pigs (n=4)	
Building renovations (n=3)	
Reduced pig density (n=2)	
Change of genetics (n=2)	
Farrowing processed slowed down (n=2)	

[a] These included autogenous vaccines against *Streptococcus suis* (n=5) and *Bordetella bronchiseptica* (n=1) and *Actinobacillus pleuropneumoniae* (n=1)
[b] These included mineral and vitamins (n=4), fat additive (n=1) and hepato-protector (n=1)
Each farm implemented one or a combination of several measures; therefore, the number of included measures is higher than the number of participating farms.

Direct net cost of the interventions

Figure 12 shows the distribution of the components of the direct net cost of the interventions. The purchase of consumables was the main contributor to the direct net cost of the intervention, followed by the visits of the herd veterinarian and other stakeholders. The direct net cost of the intervention was highly variable between farms. Three farms had consumables costs between €50 and €60 per sow per year; two of them implemented vaccination against two additional pathogens (Porcine Circovirus 2 and *Lawsonia intracellularis*), and one implemented a new vaccination against Shigatoxin Stx2e-producing *Escherichia coli.* Eight farms had a negative direct cost of intervention; three of them removed one or two indications from their vaccination scheme or switched from two-shot to one-shot vaccination. Three farms stopped castrating piglets either to produce entire male pigs (one farm) or to use boar taint vaccination (two farms); the two latter Swedish farms received subsidies from the Government as part of a national pig welfare programme (covering extra work, i.e. €0.21 per piglet, and boar taint vaccine doses). Two farms reduced their feed costs while imposing rationing in sows or fatteners.

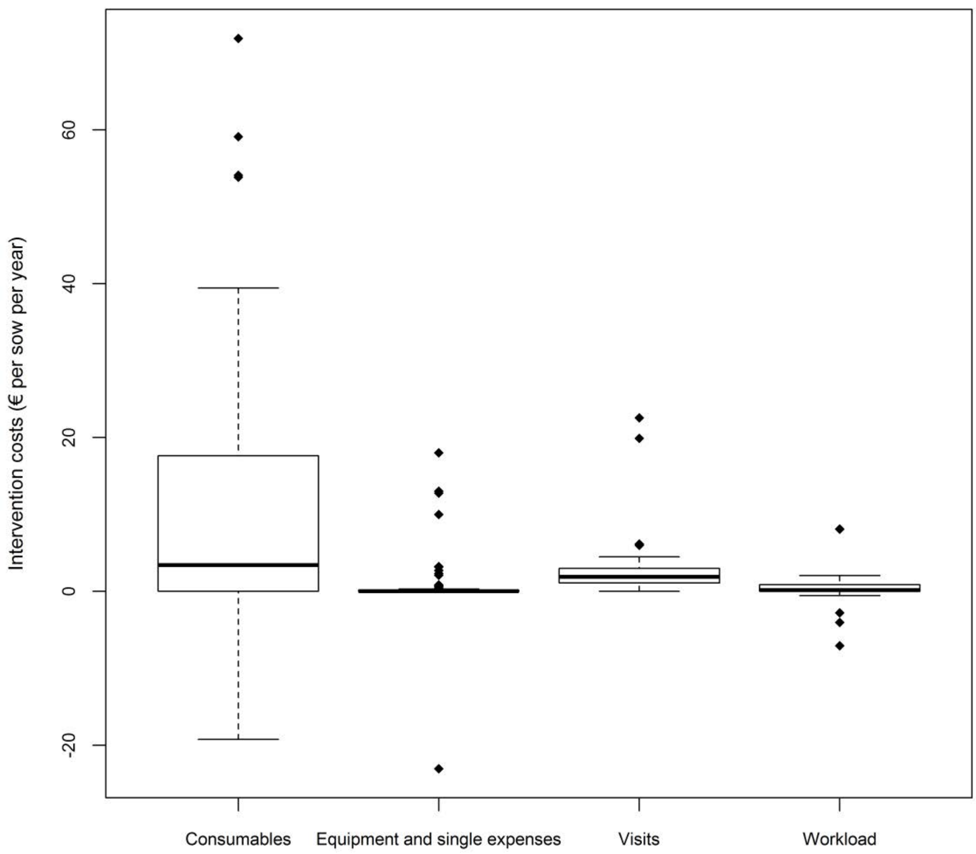

Figure 12. Distribution of the components of the direct net cost of the interventions (n=68 farrow-to-finish farms)

In case some routine activities stopped as part of the intervention, the associated purchase of consumables and workload were deducted from the costs of the intervention.

Achieved antimicrobial reduction

Following intervention, median TI200d and associated antimicrobial expenditures were significantly reduced by -47.0% and -30.5%, respectively (see Table 12). Reduction of TI200d and reduction of antimicrobial expenditures were highly correlated (Spearman's rank correlation $\rho=0.63$, $p<0.001$). Detailed description of the observed reduction of antimicrobial usage per animal category, antimicrobial class and administration route is provided by Loesken et al. (in prep.).

Table 12. Achieved reduction in TI200d and antimicrobial expenditures before and after intervention (n=67 farms)

	Median value before intervention (Q25; Q75)	Median value after intervention (Q25 ; Q75)	Corresponding relative variation (%)	p-value [b]
TI200d [a]	244.2 (80.7; 389.5)	129.5 (52.6; 249.5)	-47.0	<0.001
Antimicrobial expenditures (€ per sow per year)	33.95 (17.11; 48.69)	23.60 (13.72; 39.05)	-30.5	0.003

[a] TI200d represents the number of pigs per 1000 receiving a daily dose of an antimicrobial from birth until slaughter
[b] Significance of the paired-sample Wilcoxon test
One farm was excluded of the analysis because of incomplete antimicrobial usage data.

Association between achieved antimicrobial reduction and compliance, type of measures and direct net cost of interventions

Figure 13 shows the association between farm-level of compliance and relative TI200d reduction. Farms with high level of compliance with the predefined plan tended to achieve bigger reduction, but the association was not statistically significant (Spearman's rank correlation $\rho=-0.18$, $p=0.162$).

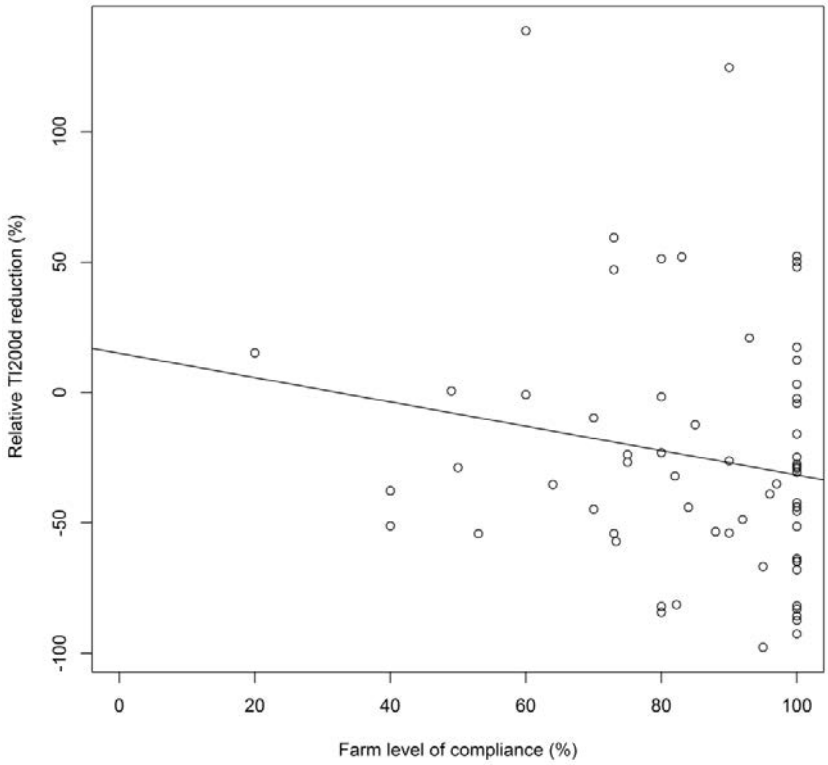

Figure 13. Association between farm-level compliance and relative TI200d reduction (n=65 farms)

Spearman's rank correlation ρ=-0.18, p=0.162.
Two outlier farms were excluded from the figure to facilitate data visualization; one farm was excluded from the analysis because of incomplete antimicrobial usage data.

Observed change in farm technical performance

Table 13 shows the change of the farm technical performance before and after intervention. No change was observed in the mortality in suckling piglets, weaners and fatteners. Daily weight gain and feed conversion ratio during the fattening period also remained stable. The number of litters per sow and per year remained unchanged, whereas the number of weaned piglets per sow and per year increased.

Table 13. Change of farm technical performance before and after intervention (n=68 farms)

Technical parameter	Median value before intervention (Q25; Q75)	Median value after intervention (Q25; Q75)	p-value [a]
Mortality in suckling piglets (%)	14.6 (11.7; 17.0)	13.9 (12.0; 17.8)	0.971
Mortality in weaners (%) [b]	2.2 (1.7; 3.0)	2.1 (1.9; 3.4)	0.906
Mortality in fatteners (%) [b]	3.0 (1.4; 4.2)	2.1 (1.5; 4.0)	0.627
Daily weight gain (g/day) [c]	761.9 (714.3; 816.3)	767.0 (715.0; 799.0)	0.980
Feed conversion ratio (kg feed/kg live weight) [c]	2.7 (2.6; 2.8)	2.7 (2.6; 2.8)	0.931
Number of litters per sow and per year [d]	2.4 (2.3; 2.5)	2.4 (2.3; 2.5)	0.369
Number of weaned piglets per sow and per year	27.2 (24.8; 28.8)	27.4 (25.2; 29.0)	0.008

[a] Significance of the paired-sample Wilcoxon test
[b] Mortality data in weaners and fatteners were not available for the German farms
[c] Daily weight gain and feed conversion ratio were not available for the German and Swedish farms
[d] Number of litters per sow and per year were not available for the Swedish farms

Results of the farm economic analysis

The farm economic analysis conducted among 33 Belgian and French farms showed a median change in net farm profit of €4.46 per sow per year (Q25: -32.54; Q75: 80.50) using the deterministic model, and €1.23 per sow per year (Q25: -31.12; Q75: 74.45) using the stochastic model respectively; both variables had normal distribution (Shapiro-Wilk normality tests equaled W=0.97, p-value=0.430, and W=0.97, p-value=0.400)). Detailed description of the farm economic analysis results for each individual farm is presented in Appendix S9. The stochastic model showed that 13 out of 33 farms increased their net farm profit by more than €25 per sow per year (Figure 14); ten of them substantially increased their margin over feed cost, whereas farm B9 and B11 substantially decreased their antimicrobial expenditures. Farm F8 slighlty increased its margin over feed cost and had negative direct net cost of intervention (imposing feed rationing in sows). Ten other farms reduced their net farm profit by more than 25€ per sow per year; for five of them, it mostly related to a substantial decrease in the margin over feed cost; farms B5, B1, F18 and F10 simultaneously experienced a decrease in the margin over feed cost and a high direct net cost of intervention; farm F2 increased antimicrobial expenditures.

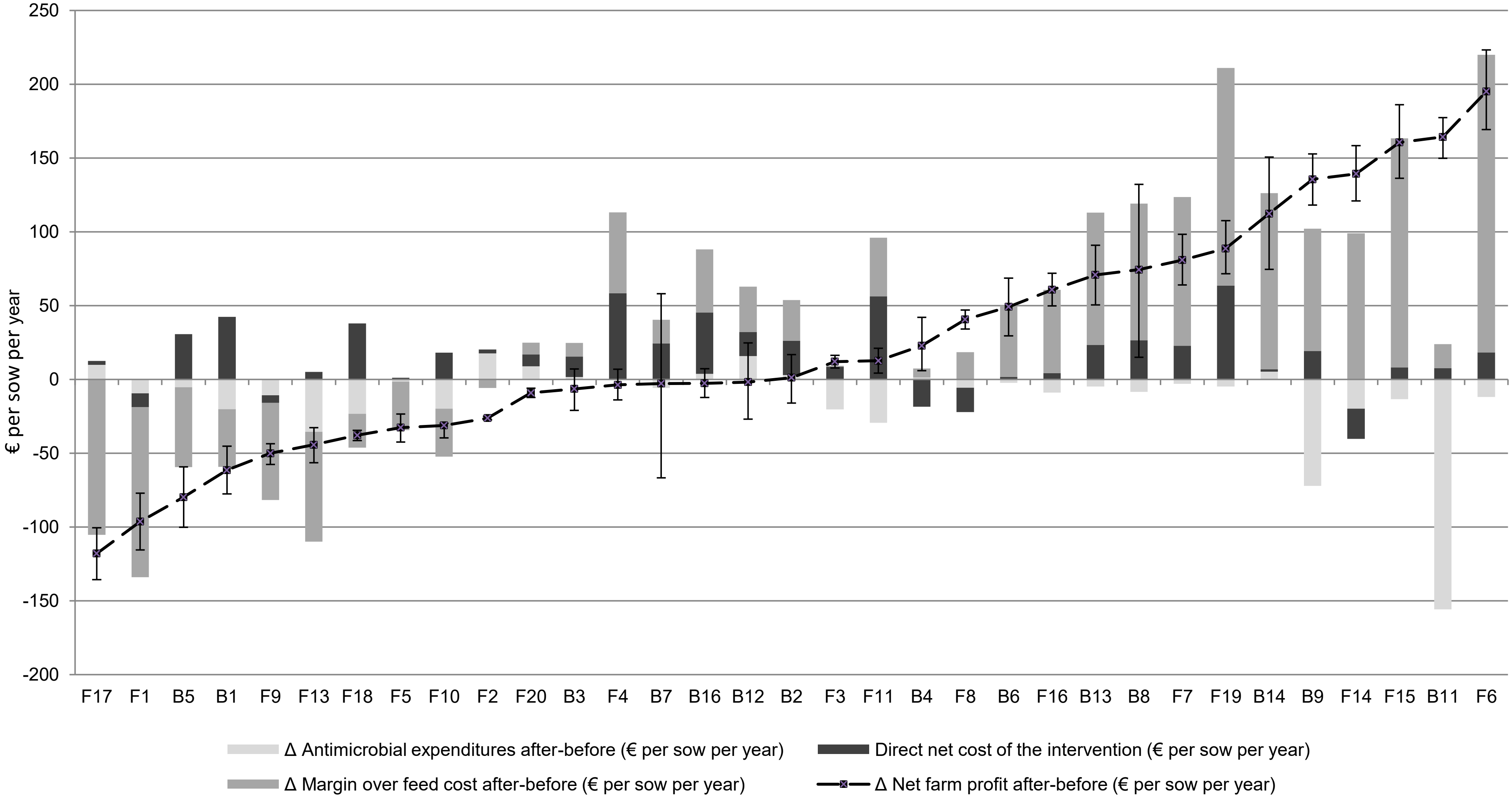

Figure 14. Results of the farm economic analysis conducted in a subset of farms in Belgium (B) and France (F) (n=33 farms)

Farms were ordered from left to right by increasing change in net farm profit. In accordance with Eq. (7), change in net farm profit was obtained by substracting the change in antimicrobial expenditures and the direct net cost of intervention to the change in margin over feed cost. Bars represent 95% confidence intervals around the mean estimate of the change in net farm profit, as estimated by the stochastic model.

The sensitivity analysis performed among Belgian and French farms showed that changes in the feed conversion ratio and daily weight gain in fatteners mostly influenced the change in net farm profit (Figure 15). Changes in farm antimicrobial expenditures and direct net cost of intervention were the third most influential variable of the Belgian and French model, respectively.

The break–even analysis showed that the overall antimicrobial prices should have been multiplied by 4.1 to increase savings on antimicrobial expenditures to a level where 90% of the French and Belgian participating farms would have a positive or zero change in net farm profit (i.e. ∆ Net farm profit $_{\text{after-before}}$ ≥0), assuming all other parameters (including demand for antimicrobial products) remain equal. The second scenario showed that finisher price should have been increased by € 0.03 per kg live weight for 90% of the Belgian and French participating farms to have a ∆ Net farm profit $_{\text{after-before}}$ ≥0, assuming all other model parameters, including the demand for pork products remain equal.

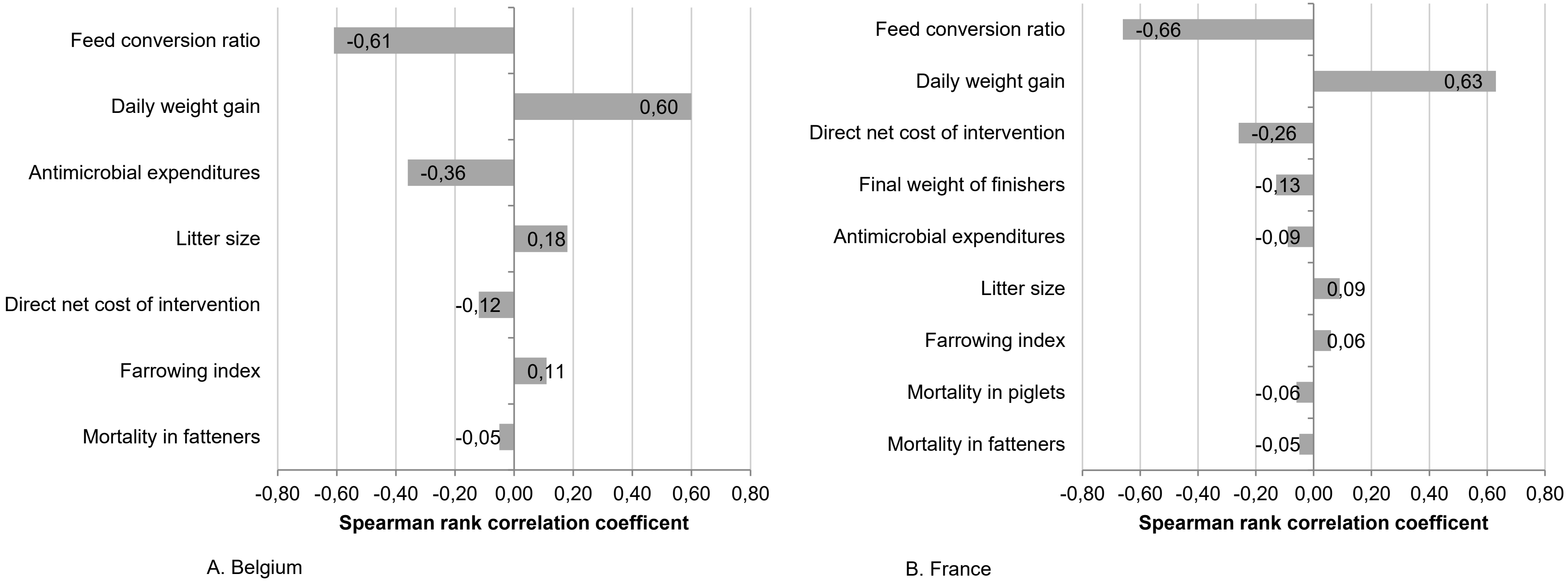

Figure 15. Tornado plot displaying the stochastic model input parameters mostly correlated with the variation of the net farm profit in A. Belgium and B. France

The Tornado plot displays the Spearman rank correlations between a given input parameter and the variation in the net farm profit, assuming all other input parameters remain constant.

5.2.5 Discussion

The present study conducted in four European countries, showed that following the implementation of herd-specific interventions, a substantial reduction in antimicrobial usage in pig farming could be achieved, without impacting the overall farm technical performance. A median reduction of 47.0% of antimicrobial usage was obtained, when expressed in terms of treatment incidence from birth to slaughter. This is in line with the results from a recent study conducted among 61 Belgian pig farms, where treatment incidence from birth to slaughter was reduced by 52.0% (Postma et al., 2016a). Farms with higher compliance with the intervention plan and higher direct net cost of intervention tended to achieve bigger reduction, but the associations were not significant. This might be because most herds had a very high compliance (e.g. only 5 herds had a compliance ≤50%), consequently reducing the ability to detect a significant association. Similarly, direct net cost of intervention had limited variability (43% of the herds had direct net cost between €0 and €10 per sow per year). In addition, while the direct net cost of intervention quantified the financial investment made by the farmer to implement the measures, it could not capture the suitability and relevance of the intervention to reduce antimicrobial usage at a given farm, and therefore was only a poor predictor of the achieved reduction. No correlation was observed between the type, category or number of implemented measures and the achieved reduction of antimicrobial usage. Although we cannot exclude this was related to the rather small study sample size and the diversity of proposed measures, it appeared evident that no single measure could be identified as the ‘golden bullet’ for reducing antimicrobial usage in any herd. On the contrary, tailored made, herd-specific interventions that perfectly match the farm needs to improve pig health are needed.

Overall, herd technical performance did not differ before and after intervention. However, the farm economic analysis conducted in a subset of Belgian and French herds showed high between-herd variability of the variation in the farm net profit. Similar observations were previously made by Rojo-Gimeno et al. (2016); in the latter study, an increase of average farm profit of €42.99 (CI 95% -79.13; 151.43) per sow per year was observed following the implementation of the interventions. However, the results are not directly comparable with those from this study, as study designs used in both studies substantially differed. Rojo-Gimeno et al. (2016) used a propensity score analysis to match intervention herds with control herds obtained from the European Farm Accountancy Data Network (http://ec.europa.eu/agriculture/rica). The main advantage of this approach is that it allows assessing the success of the intervention independently from any external changes (e.g. national programmes for reducing antimicrobial usage or genetic improvement of technical performance over time). However, matching criteria were limited to a reduced number of herd characteristics, i.e. number of sows and employees, age of the oldest building and farmer’s year of experience with pig farming. In the present study, it was decided to consider each farm as its own control, and to compare them before and after intervention. This decision was made because detailed data were already available from a previous cross-sectional study, and because of the difficulty to define proper control herds. Indeed, pig farms keep constantly changing and adjusting their management practices to the new production and health context they are facing. It makes it almost impossible to identify farms ‘not changing’ their practices, even in the short course of one year.

We cannot exclude, however, that part of the observed reduction in antimicrobial usage could be related to other factors than the implemented measures. In Belgium, the AMCRA is actively promoting the rational use of antimicrobial in farm animals, and has set clear reduction targets for coming years, including a 50% lower antimicrobial use by 2020 when compared with 2011 (http://www.amcra.be/). Total sales of veterinary antimicrobials in Belgian farm and companion animals had been decreasing steadily by 12.7% between 2011 and 2013, when expressed in mg of active substance per kg biomass. However between 2013 and 2014 (i.e. the period of the present study), the total sales increased by 1.1% (BelVet-SAC, 2014). This increase was attributed to a relaxed attitude of stakeholders involved towards responsible and restricted antimicrobial use during this particular year (BelVet-SAC, 2014).

France also has a national action plan against the rising threat of antimicrobial resistance (French Ministry of Agriculture, 2012), and aims to reduce veterinary antimicrobial usage by 25% between 2013 and 2017. The total volume of antimicrobials sold for pigs in France has been falling steadily in the recent years, with 27.7% reduction between 2009 and 2013; however, the volume sold for pigs in 2014 increased by 6.1% when compared with 2013 (Anses, 2015), likely as a result of a change in the French legislation that introduced an end to discounts, rebates and reductions on antimicrobials, with effect from 1 January 2015 (Act no. 2014-1170 of 13 October 2014 on the future of agriculture, food and forestry). It seems indeed, that this prospect paradoxically led stakeholders involved in veterinary medicinal product distribution and/or prescription to accumulate stocks of medicines containing antimicrobials at the end of 2014 (Anses, 2015).

In Germany, the national monitoring of veterinary antimicrobial sales data showed a 14.9% reduction in the amounts (in tons of active substance) of antimicrobials sold for animals by between 2011 and 2013, and a 14.7% reduction between 2013 and 2014 (GERMAP, 2015). In Sweden, sales of antimicrobials for pigs have been stable over the last years (these were estimated to be 12.8 and 12.1 mg/kg slaughtered pig in 2010 and 2015, respectively (SWEDRES-SVARM, 2015)); however, one should remember that veterinary antimicrobial usage in Sweden is among the lowest in Europe (European Medicines Agency, 2015). A number of other initiatives, including from the industry, also encourage the reduction of antimicrobial usage in pig production. These likely influenced the reduction observed in participating farms, and might have led to an over-estimation of the effect of the implemented intervention plans. Similarly, the very slight improvement observed in the number of weaned piglets per sow and per year might partially come from the genetic improvement of sows' fertility over the years (IFIP 2016). However, because genetic improvement of herd performance over time is a rather slow process, this effect was probably not captured in the short course of the present study.

The farm economic analysis could only be conducted in 33 Belgian and French herds, because of the difficulty to collect technical performance data, especially growth performance, in the remaining herds. Especially daily weight gains and feed conversion ratios could not be collected in the German herds, even in a prospective way. These data should definitely be collected routinely to improve the assessment of similar intervention studies in the future. The farm economic analysis conducted in this study still highlighted interesting results. It showed in particular that the change in net farm profit was much more influenced by the change in margin over feed cost than by the direct net cost of intervention or the change in antimicrobial expenditures. Additionally, the change in margin over feed cost was mostly correlated with the change in daily weight gain and feed conversion ratio during the fattening period. It means that farms that did manage to maintain or improve their daily weight gain and feed conversion ratio while reducing antimicrobial usage overall had a more economically successful intervention. However, the observed changes in daily weight gain and feed conversion ratio might have been independent from the implemented measures.

Approximately half of the Belgian and French farms had an improvement in net farm profit after the intervention and 70% of them had a change in net farm profit >€-10 per sow per year. Two possible economic incentive measures for farmers to reduce their antimicrobial usage were explored using break-even analysis. The overall antimicrobial prices should have been multiplied by 4.1 to increase savings on antimicrobial expenditures to a level where 90% of the farms would get a positive or zero change in the net farm profit, assuming all other parameters remained equal; this scenario seemed rather unrealistic. Additionally, finisher price should have been increased by € 0.03 per kg live weight for 90% of the farms to get a positive or zero change in the net farm profit, assuming all other parameters remained equal. This scenario appeared more realistic, but was based on the crude assumption that the demand for pork products would remain equal. More studies are needed to explore how much consumers would be willing to pay for pigs raised with minimal antimicrobial treatments. Incentive economic measures could indeed be considered by the pig industry or national authorities to further encourage farmers to reduce their usage, and therefore contribute to the achievement of national reduction targets. However, the present study showed that it was possible to achieve substantial reduction in antimicrobial usage without impacting the average herd performance and net farm profit. The question of whether economic incentives are actually needed is therefore debatable. In addition to economic factors, other factors should also be considered to make farmers actually change their practices; especially the advisory role of the herd veterinarian and herd technicians should be reinforced to further encourage farmers to reduce their antimicrobial usage and implement alternative measures (Speksnijder et al., 2015; Visschers et al., 2016).

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5.3 Conclusion of the chapter

The objective of this Chapter was to assess the technical and economic impact of alternative measures to antimicrobial treatments in pig production. It was shown that following the implementation of herd-specific interventions, with high compliance with recommended measures, a substantial reduction in antimicrobial usage could be achieved. On average, this reduction did not come at a cost on the farm technical performance or the net farm profit, but the observed variability was relatively high. Especially farms that managed to maintain or improve their growth performance had a more economically successful intervention. The achieved reduction in antimicrobial usage was independent from the number or type of implemented measures; it means that there is no 'golden bullet' to reduce antimicrobial usage at herd level. Tailor-made interventions should be developed to prevent or control the health or production problems of the particular farm under study, subsequently reducing the need for antimicrobial treatments at this farm. The advisory role of key stakeholders, and especially veterinarians, should be reinforced so that they are able to identify what are the drivers for antimicrobial usage in a particular farm, what are the most promising alternative measures and how to engage farmers to implement them.

CHAPTER 6: GENERAL DISCUSSION AND PERSPECTIVES

Recognizing the importance of AMR as a global threat for public health, a number of initiatives have been developed at international, European and national levels in order to mitigate the risk associated with AMR. One of the main objectives of the current strategies is to reduce the use of antimicrobials in food-producing animals, and especially in pig production, which is one of the sectors with the highest antimicrobial use. Key activities include the promotion of the responsible use of antimicrobials, the development and adoption of alternative strategies to antimicrobial treatments, and the monitoring of antimicrobial use to assess the impact of the mitigation strategies. These strategies however, are facing a number of challenges and information gaps. The objective of this PhD was to address some of these challenges and information gaps, by exploring more specifically how to best quantify antimicrobial use, what are the key drivers for antimicrobial use in food-producing animals, and what is the technical and economic impact of existing alternatives to antimicrobial treatments.

Below are presented and discussed the key findings of this PhD thesis, the difficulties and challenges that were encountered and the data gaps that remain, as well as possible options to address them, in order to move forward in the reduction of antimicrobial use in food-producing animals. Future perspectives of the reduction of antimicrobial use in food-producing animals are also discussed.

6.1 Quantifying antimicrobial use

6.1.1 Key findings

From the work presented in this thesis, it has become very clear that when introducing a policy or implementing a monitoring programme on antimicrobial use in food-producing animals, one should think carefully about the best way to quantify antimicrobial use. Typical questions that arise are where to collect the data, from which sources, what data should be recorded and what indicator or unit should be calculated to be able to interpret and make the best use of collected data. The answer is not straightforward as many different approaches have been developed both in human and veterinary medicine, and the choice of a given approach can lead to different, even contradictory conclusions.

The two most common approaches that have been used so far consist in either collecting high-level antimicrobial use data, typically total weights of antimicrobials sold in a year for veterinary usage as reported by the manufacturers or wholesalers, or to collect detailed herd-level antimicrobial use data from a limited number of farms, as this was done in the MINAPIG project. The former has the advantage of being comprehensive, objective and easy to communicate; however, one can hardly identify how (e.g. what dose, duration), by whom (e.g. what animal species, production category, age group) and for what indication (e.g. preventive, metaphylactic or curative) the antimicrobial treatment was used. The later provides more accurate information on the way antimicrobials were used, but can hardly be comprehensive and therefore raises the question of the representativeness of the sample being investigated. For example, representativeness was certainly a limitation of the MINAPIG cross-sectional study (see Chapters 3 and 4); only farmers who agreed to participate were involved in the study, which likely introduced some kind of selection bias. Of course, many 'intermediate' approaches are available and rely, for example, on data collection among retailers, pharmacies, feed companies or veterinarians.

To the question 'how to best quantify antimicrobial use in food-producing animals', we strongly emphasized, in Chapter 2, that the most suitable approach should be informed by the study objective. Indeed, whether the study is aiming at monitoring antimicrobial use over time, comparing use between different species or countries, benchmarking farms or veterinarians, or exploring the association between antimicrobial use and resistance implies a number of requirements on the way antimicrobial use should be quantified. If the aim is to monitor antimicrobial use over time, it is crucial to use a robust quantification system that allows stability over time in terms of required data and provided output; to compare usage between different species or countries, comparability must be ensured between the different populations. If data are used for benchmarking, the system comprehensiveness is particularly crucial, while data collected to study the association between antimicrobial use and resistance should express the exposure level and duration as a measurement of the exerted selection pressure.

Recommendations on the most suitable indicators of antimicrobial use for a given study objective were provided in Chapter 2. Using currently available data, it was however not possible to give recommendations on a single indicator that would perfectly suit a given objective. This may actually not be necessary, as the calculation of several indicators from the same data was shown to provide complementary information. For example, the French annual report on veterinary antimicrobial sales data presents results expressed both in terms of total weight of active substance sold in a year, which can be used for multi-country comparison and to monitor trends over time, and in terms of ALEA, an indicator used in France to assess the level of exposure of animals to antimicrobials (Anses, 2015).

As part of the MINAPIG cross-sectional and intervention studies, it was decided to quantify antimicrobial use in terms of treatment incidence. Computing this indicator was informative and suitable for multi-country comparison, but it required beforehand to agree on standard weights at treatment, production lengths and daily doses. Especially daily doses as recommended by the SPC substantially differed between the four participating countries; such discrepancies were rather unexpected and later published by Postma et al. (2015a). Besides, because the treatment incidence expresses a percentage of animals daily treated, or a percentage of their life expectancy animals are treated with antimicrobials, strong emphasize was put on group treatments, and treatments of long duration (e.g. oral treatments via feed or water). The choice of another indicator (e.g. describing the number of treatment courses) would certainly have influenced the interpretation of our results.

6.1.2 Major data gaps and challenges

The appropriate quantification of antimicrobial use in food-producing animals is facing several challenges. First, data availability and accessibility are an issue. As highlighted, many countries worldwide still have no system in place for the quantification of antimicrobial use in animals (Diaz, 2013), and the importance of over-the-counter sales of antimicrobials makes it impossible to trace forward how antimicrobial drugs are used (Morgan et al., 2011). In Europe, total amounts of antimicrobials sold for food-producing animals are usually available, at least for countries participating to the ESVAC project (European Medicines Agency, 2015), but these are a very crude measure of actual antimicrobial use, especially because they do not take into account the differences between doses of antimicrobials substances. In Chapter 2, we showed that using a succession of simple calculation steps, antimicrobial sales data can be converted into other technical units of measurements that are more informative in terms of antimicrobial use and level of exposure to antimicrobials. This requires however, reaching an agreement on the definition of the calculation parameters, e.g. daily doses, weight at treatment and treatment length. The European Medicines Agency is working in this direction; for example a first standardized list of DDDvet and DCDvet for pigs, cattle, broilers and cows was released in April 2016 (European Medicines Agency, 2016a). These more advanced quantification methods also require antimicrobial use data to be collected per animal species; such approach is not yet implemented in all European countries (Pinto Ferreira and Stärk, 2016). Antimicrobial data accessibility was also an issue during the MINAPIG study; because no participating country had automated data collection system in place, antimicrobial use data were retrieved from paper-based treatment records and expenditures, which required a tremendous effort to collect the data, verify them together with the farmer, and enter them in a database for further analysis.

Even when comprehensive and detailed antimicrobial data are available, it can be difficult to identify the most suitable indicator of antimicrobial use to be selected. This is especially true when one is quantifying antimicrobial use to study the association between exposure to antimicrobials and AMR. Today, little is known about which of the exposure characteristics, e.g. antimicrobial spectrum of the compound used, frequency of exposure, duration of exposure, level of dose or route of administration is most influential in terms of the selection pressure exerted. An increasing number of studies has been addressing these questions, exploring for example the effect of administration route (Varga et al., 2009; Zhang et al., 2013), antimicrobial dose (Vasseur et al., 2014), number of treatment courses (Costelloe et al., 2010) or treatment duration (D’Agata et al., 2007) on the selection and spread of AMR, but further input from the field of pharmacodynamics is clearly needed, especially in veterinary medicine (Rybak, 2006; Ferran et al., 2013). This will facilitate the selection of the most appropriate exposure measurements to incorporate into the quantification systems.

Another challenge relates to the definition of the objectives of antimicrobial use monitoring. While Chapter 2 emphasized the need to define beforehand the main objective of antimicrobial quantification studies to be able to select the most appropriate quantification method, one should recognize that antimicrobial monitoring can pursue several objectives simultaneously. For example, a national monitoring system could be aiming at assessing antimicrobial use trends and comparing national use with other countries. Developing a specific monitoring system for each objective would come at a very high cost. To tackle this issue, one could consider, among others, promoting the development of complementary monitoring systems (e.g. combining national data collected by Government and herd-level data collected by industry) or developing advanced monitoring systems that could properly address several objectives, i.e. using automated data collection at high resolution to compute more accurate indicators; this is the way antimicrobial monitoring is currently evolving in Europe.

6.1.3 The way forward

International organizations are working towards the improvement of the accessibility to antimicrobial use data. The FAO Action plan on AMR 2016-2020 identified the development of capacity for surveillance and monitoring of antimicrobial use in agriculture, and the strengthening of governance related to antimicrobial use as key focus areas (FAO, 2016). The OIE is currently establishing a global database on consumption of antimicrobials in animals (Freischem and Diaz, 2015).

In Europe, the revision of the EU regulation on veterinary medicinal products will likely introduce a requirement to collect antimicrobial use data per species (European Commission, 2014). The draft ESVAC Vision and Strategy 2016-2020 published in April 2016 confirmed that the European Medicines Agency is already working in this direction (European Medicines Agency, 2016b) and encourages the development of automated continuous data collection of antimicrobial use data from electronic prescriptions or delivery records. Because such advanced systems will require years to be fully operational in all ESVAC partner countries, an interim approach was proposed to stratify antimicrobial sales per species, as this is already done in some European countries, e.g. France (Anses, 2015). The ESVAC is also moving towards more standardized and harmonized methods to quantify antimicrobial use (e.g. using standardized DDDvet and DCDvet (European Medicines Agency, 2016a)). This should facilitate, in the future, the joint analysis of antimicrobial use and AMR data in humans and animals (ECDC/EFSA/EMA, 2015), and better inform risk mitigation strategies.

European and international initiatives should not prevent national countries to develop their own monitoring systems. For example, herd-level data collection of antimicrobial use has been in place since 2000 in Denmark (Stege et al., 2003), 2011 in the Netherlands (SDa, 2015) and 2014 in Germany (Federal Government of Germany, 2015). Few developing countries (e.g. Kenya, see (Kariuki, 2011)) also developed their own monitoring initiatives; to our knowledge, these mostly relied on data collection at national level (e.g. import data). More initiatives to monitor antimicrobial use are also being developed by the industry, e.g. Belpork in Belgium (www.registreab.be) or QS Company (www.vetproof.de) in Germany. One of the most noticed initiatives from the industry was the Global Vision for Antimicrobial Stewardship in Food Animals released by McDonald's in March 2015, where McDonald's engaged, among other actions, to prohibit the use of any medically important antimicrobials for growth promotion in food animals, and place the use of antimicrobial classes authorized both in human and veterinary medicine under veterinary oversight (McDonald's Corporation, 2015). McDonald's dedicated suppliers will have to maintain records of antimicrobial use and document compliance which will be verified by third party audits.

6.2 Explaining antimicrobial use

6.2.1 Key findings

Previous literature had shown that antimicrobial use in food-producing animals is influenced by a range of drivers, including herd characteristics (e.g. herd size, farrowing rhythm, weaning age), biosecurity level, farm performance, occurrence of clinical signs and vaccination scheme, as well as the farmer's attitudes and habits towards antimicrobial use. So far, the effect of these drivers had mostly been investigated separately, and little was known about their relative importance in the explanation of antimicrobial use. Because data related to all these drivers were collected in the sample of 207 farrow-to-finish farms that participated in the MINAPIG cross-sectional study, we were able to investigate the relative importance of these categories of drivers in the explanation of antimicrobial use (Chapter 3). To that end, an innovative approach called multiblock partial least squares (*mbpls*) analysis was used where potential drivers could be grouped together into meaningful categories or 'blocks' of variables, so that not only the relative effect of individual drivers, but also the relative effect of explanatory blocks could be explored. This analysis showed that the contribution of herd characteristics, biosecurity level, farm performance, occurrence of clinical signs and vaccination scheme, as well as the farmer's attitudes and habits towards antimicrobial use were relatively balanced in each participating country, and each category of drivers contributed to explaining antimicrobial use in at least one country. The occurrence of clinical signs was one of the main drivers for antimicrobial use in all four participating countries, which confirmed that antimicrobials were mostly used for the treatment of clinically sick animals (e.g. metaphylactic or curative treatments), rather than for prevention (Anses, 2014). Especially the occurrence of respiratory signs in fatteners was a significant driver for antimicrobial use in Belgium, France and Germany. This was further confirmed in Chapter 4 where farms with lower occurrence of respiratory signs in fatteners had higher chance of belonging to the group of 'top-farms' that had both low antimicrobial usage and high technical performance. Unfortunately the actual infectious status of participating farms regarding the main respiratory pathogens was not collected as part of the MINAPIG cross-sectional study, but the high proportion of farms that were vaccinating against PRRS in Belgium, France and Germany (82%, 64% and 87%, respectively), and against swine influenza and *Actinobacillus pleuropneumoniae* in Germany (85% and 35%) (see Chapter 3) suggested these farms might actually use a combination of antimicrobial treatments and vaccination to control these diseases. On the contrary, no association was observed between the occurrence of respiratory signs in fatteners and antimicrobial use in Sweden; Sweden indeed has a very high health status regarding respiratory infectious diseases; for example it is free of PRRS (Frössling et al., 2009).

Similarly, the influence of biosecurity on antimicrobial use was low in Sweden compared to the other participating countries (Chapter 3). Again, this could be related to the high health status of Swedish farms compared to the other countries, and to the fact that Sweden has lower pig density (Postma et al., 2016). Chapter 4 indeed showed that across all four countries, farms with higher internal biosecurity (especially regarding disease management and farm compartmentalization) and higher external biosecurity (especially regarding farm environment and region) had higher chance of being in the top-farms group. The positive effect of biosecurity could be weaker in Sweden where the risk of introduction of infectious diseases and subsequent spread within the farm is lower.

The association between antimicrobial use and farm technical performance was hard to assess with the multiblock regression analysis (Chapter 3); because of the cross-sectional design of the study, it was indeed difficult to distinguish farms relying on antimicrobials to control diseases and have better performance, from those farms with high performance where antimicrobial treatments were not needed because of a high health status. The definition of a top-farms group that had both low antimicrobial use and high performance (Chapter 4) helped to overcome this issue. The intervention study also confirmed that technical performance could be kept stable even after a substantial reduction of antimicrobial use was achieved (Chapter 5).

The effect of herd characteristics on antimicrobial use was highly variable between countries. Chapter 3 showed that bigger farms had higher antimicrobial use in Germany and Sweden, but this effect was not significant in the other countries. Swedish farms with higher weaning age had lower antimicrobial use (Chapter 3), but farms with higher weaning age also had lower chance of being in the top-farms group, especially within the subgroup of farms located in high-density areas (Chapter 4); it suggests weaning age influences both antimicrobial use and technical performance, especially when expressed in terms of number of weaned per sow per year.

Previous MINAPIG research conducted across all four participating countries had shown that farmer's attitudes and habits towards antimicrobials and AMR significantly influenced antimicrobial use at their farm (Visschers et al., 2016a), as well as the farmer's intentions to reduce their antimicrobial use (Visschers et al., 2016b). Chapter 3 showed that this effect could differ between countries; compared to the other selected categories of drivers, the relative contribution of farmer's attitudes and habits to the explanation of antimicrobial use was high in Sweden and Belgium, lower in France and null in Germany. Further work is needed to explain those differences; one hypothesis might be that pig production is highly integrated in Germany; treatments procedures are therefore more likely to be standardized (Schulze, 2006).

While Chapter 3 and 4 highlighted that drivers for antimicrobial use differed between countries, one should also keep in mind that drivers for antimicrobial use are also likely to differ between farms, even within the same country. This idea was mostly illustrated in Chapter 5, where farm-specific issues in relation to pig health, farm management, as well as farmer's attitudes (e.g. risk aversion) first had to be investigated in details before being able to define an intervention that could potentially reduce antimicrobial use in that particular farm. This reinforces the importance of the role of the veterinarian and other farm advisors as key stakeholders in the reduction of antimicrobial use in animals (European Commission, 2011).

6.2.2 Major data gaps and challenges

One of the main challenges that was faced when investigating the main drivers for antimicrobial use from the MINAPIG cross-sectional study was related to the fact that participating countries had very different levels of antimicrobial use. Especially Sweden had much lower antimicrobial use than the three other countries, and Germany had higher use than Belgium and France, as previously shown by Sjölund et al. (2016) (see Figure 3 in section 1.4.4).

The *mbpls* method we used in Chapter 3 did not allow controlling for the country effect; therefore, when a multi-country model was initially developed including the country of origin as a driver among others, the country of origin contributed to 33% of the observed variation in antimicrobial use. It means that on top of all the potential explanatory drivers that were considered, the country of origin had a major contribution to antimicrobial use. Factors associated with the country of origin could include, among others, differences in national regulations on antimicrobial use. For example, Swedish veterinarians can only prescribe antimicrobial drugs but not sell them, at the difference of Belgium, France and Germany. Also, Sweden has a long tradition for the restriction of antimicrobial use in animals, and was the first European country to introduce a ban on antimicrobial growth promoters in 1986 (Wierup, 2001). Cultural differences could also play a role, for example in relation with how people are using antimicrobials to treat themselves (i.e. antimicrobial treatment practices in human medicine). Because of the importance of the country effect, it was decided to rather develop four country-specific models, and to explore the relative contribution of the different categories of drivers for each country separately. The small sample size of country-specific models was not an issue to explore the relative contribution of drivers or categories of drivers, but certainly reduced our ability to detect significant effects in the model assessing the associations between drivers and individual response variables (i.e. exploratory analysis conducted in France). Similarly in Chapter 4, country-specific cut-off values had to be used to be able to select the top-farms with low antimicrobial use and high technical performance from each participating country; this approach was used to make sure the top-farms group was representative from all four countries.

Additionally, the *mbpls* did not provide an estimate of the overall significance of the model. Although a wide range of potential explanatory drivers was included in the model, other relevant drivers could also have been considered. As already mentioned in the previous section, the herd actual infectious status regarding main infectious agents, especially respiratory agents would certainly have contributed to further explaining antimicrobial use, although this aspect was partially captured by the occurrence of clinical signs and vaccination scheme. Other technical drivers, e.g. in relation to the housing conditions of the pigs (e.g. age and type of buildings) could also have been explored further, as these were previously described as significant risk factors for high antimicrobial use (Chauvin et al., 2005). Similarly, other psychosocial drivers could have been considered; for example, the advisory role of the veterinarian as perceived by the farmer was included, but the rationale of the herd veterinarian for prescribing antimicrobials could have been investigated in more details, as it was shown to be highly variable between veterinarians and to strongly influence antimicrobial use (Speksnijder et al., 2015a; Coyne et al., 2016).

6.2.3 The way forward

From the lessons learnt in Chapters 3 and 4, it clearly appeared that a wide range of technical and psychosocial drivers simultaneously influence antimicrobial use in pig farming. Especially Chapter 4 showed that none of the different categories of drivers could be identified as being much more influential than the others; on the contrary, their relative contribution was relatively balanced in each country. These findings support the holistic approach which has been promoted so far by national, European and international action plans to tackle the risk associated with AMR (European Commission, 2011; World Health Organization, 2015). This means that interventions should consider the diversity of herd characteristics, biosecurity levels, farm performance, clinical health situation and vaccination schemes, as well as the farmer’s attitudes and habits towards antimicrobial use.

Additionally, the relative contribution of the selected categories of drivers differed from one country to another indicating a need for policies tailored to national needs. These country-specific features should therefore be considered when prioritizing future national risk mitigation activities. For example, the implementation of strict biosecurity practices appeared as a key driver for reduced antimicrobial use in Belgium, France and Germany, but the positive effect seemed lower in Sweden where health status is very high and pig density lower. The occurrence of clinical signs was a key driver in all four countries, which confirmed that more emphasis should be put on the prevention and control of infectious, especially respiratory diseases in the future. This is in agreement with the motto ‘Prevention is better than cure’ promoted by the EU Animal Health Strategy 2007-2013 and the new EU Animal Health Law (European Commission, 2007; EU Regulation 2016/429). Additionally, because drivers for antimicrobial use also differed between farms, even within the same countries, the abilities of veterinarians and other farm advisors to identify farm-specific barriers (e.g. pig health, farm management issues or farmers’ attitudes) to the reduction of antimicrobial use should be strengthened.

6.3 Assessing the impact of alternatives to antimicrobials

6.3.1 Key findings

Chapter 4 showed that following the implementation of herd-specific interventions, a substantial reduction in antimicrobial use could be achieved in pig production, without impacting the overall farm technical performance. Across all 70 farrow-to-finish herds that participated in the MINAPIG intervention study, a median reduction of 47.0% of antimicrobial use was obtained when expressed in terms of treatment incidence from birth to slaughter, corresponding to a 30.5% median reduction of antimicrobial expenditures. A wide range of alternative measures was initially considered, including reinforced biosecurity, vaccination, use of feed additives, changes in feeding schemes or drinking water quality, improved pig management, health care, welfare and housing conditions (Postma et al., 2015b). In the end, most commonly selected measures were not the most innovative ones, but rather classical and well-known good pig farming practices (e.g. good hygiene procedures, strict all-in all-out, climate improvement) and preventive measures (mostly vaccination).

The first visit during which the intervention was defined together with the farmer, the herd veterinarian, other advisor (when relevant) and the MINAPIG researcher was a critical step in the intervention procedure. The farmer had to be convinced that the proposed measures would be both feasible, effective and with no impact on his/her pig health and technical performance to guarantee future compliance with the plan. This was only made possible by defining tailor-made interventions. The compliance observed in the MINAPIG interventions was high (median: 93%; min-max: 20-100) and farms with higher compliance tended to achieve bigger reduction. Compliance was certainly positively influenced by the fact that farmers were aware of being part of a research study, and therefore closely monitored; however, strict monitoring should also be considered as a requirement for future similar intervention studies to be successful, even in a research-independent context. Compliance was reduced when the number of measures increased; it means that interventions should better focus on a limited number of measures, or at least categorize those measures that should be implemented with high, medium and low priority.

On average, no change in the farm technical performance and a minor increase in the net farm profit were observed before and after intervention. However, between-farm variability was high and the before/after design of the intervention study made it difficult to interpret whether an observed change in farm technical performance or net farm profit could be attributed to the intervention only, or whether external factors also had an impact. Similarly, the observed reduction in antimicrobial use could have been partly related to factors independent from the MINAPIG intervention, e.g. Government or industry initiatives. Still, the MINAPIG intervention study provided concrete examples to illustrate that a substantial reduction of antimicrobial use could be achieved without jeopardizing technical and economic performance.

The change in net farm profit was mostly influenced by changes in growth performance (i.e. daily weight gain and feed conversion ratio), rather than by the costs of implemented measures or the savings associated with the reduction of antimicrobial expenditures. It means the costs of the alternative measures should not be perceived as a barrier, as long as they contribute to maintain or improve growth performance. On the other hand, potential savings on antimicrobial expenditures did not appear as a strong incentive to reduce antimicrobial use, at least with current antimicrobial prices. A simple scenario developed in Chapter 5 showed that overall antimicrobial prices should be multiplied by 4 to increase savings on antimicrobial expenditures to a level where 90% of the participating farms would have a positive or zero change in net farm profit, assuming all other parameters (including demand for antimicrobials) remain equal. Such measure seemed rather unrealistic. Another economic incentive could consist in offering premiums to farmers producing pigs with reduced antimicrobial treatments. This idea was also explored further in Chapter 5, and it was shown that finisher price should have been increased by € 0.03 per kg live weight for 90% of the participating farms to have a positive or zero change in net farm profit, assuming all other parameters (including demand for pork products) remain equal; this measure seemed more realistic and could be considered by industry or Government as an economic incentive to further reduce antimicrobial use.

6.3.2 Major data gaps and challenges

Several difficulties were encountered when investigating the technical and economic impact of alternatives to antimicrobials. First, the availability and reliability of technical performance data were an issue. It seems many herds, especially German and Swedish herds, do not record technical performance data in routine, including critical data such as feed conversion ratio or daily weight gain, that are known to strongly influence the net farm profit. Even collecting these data in a prospective way was not possible in many herds. This was a serious limitation of our study, and as a consequence, the full economic assessment could only be performed in 33 Belgian and French farms. Availability and reliability of technical performance data should definitely be improved in future similar studies.

Another challenge related to the definition of a control group for the intervention study. It was initially considered to match intervention herds with control herds where no intervention would have been implemented. However, it was felt extremely difficult to identify proper control herds, as these would have to be comparable with intervention herds in terms of health status, vaccination scheme, management practices, i.e. all those drivers that were previously identified in Chapters 3 and 4 as influencing antimicrobial use. A very strong confounding effect was expected. It was therefore decided to rather use each intervention herd as its own control. However, this made it difficult to distinguish the effect of the intervention from the effect of other external factors. The follow-up period was relatively short (a one-year period with intervention was compared with a one-year period before intervention), which probably reduced our ability to detect differences (type II error). It would certainly be interesting to conduct similar follow-ups over a longer period of time, especially to assess whether antimicrobial use can still be maintained at low levels with no impact on performance. One difficulty of longer follow-up periods would be, however, that farmers keep regularly changing their management practices and after a certain period of time, it becomes difficult to define an intervention as a ‘unique’ entity; it rather becomes a combination of measures that were implemented at some point and later removed.

In the MINAPIG intervention study, every herd was implementing a different intervention, both in terms of number and type of measures that were implemented; sample size was also relatively small (70 herds in total); it was therefore impossible to assess the impact of an individual measure, e.g. vaccination against a specific pathogen. Conducting such an assessment would anyway be of limited value, because a measure which is effective in a particular herd would not necessarily be effective in another herd with different production environment or health status. An intervention to reduce antimicrobial use should rather be considered as a more-or-less unique combination of herd-specific measures. This intervention should, as far as possible, prevent or control the specific health or production problems of the particular farm under study. As a consequence the need for antimicrobial treatments should then be reduced.

6.3.3 The way forward

The MINAPIG intervention study was conducted among a limited number of pig farmers that volunteered to participate and are therefore likely to represent a biased sample. They were likely to be interested in the topic of antimicrobial use and AMR and may be above-average in general aspects of farm and animal health management. This raises the question of how to upscale similar approaches, particularly if involving farmers who are more reluctant to reduce their antimicrobial use and implement alternative measures.

Some countries have implemented a legal basis that obliges farmers who’s antimicrobial use is above a certain threshold to take active measures. Such policy is already in place in several European countries, including Denmark, where the so-called ‘Yellow card’ initiative (Danish Veterinary and Food Administration, 2010) was introduced in 2010. Danish farmers above the acceptable threshold for antimicrobial use have to take active measures within a 9-month period, or otherwise are placed under increased supervision and may receive a ‘red card’. A similar approach was implemented in the Netherlands in 2011, with a system of traffic lights where farmers in the ‘action zone’ (i.e. red zone) should take active measures to reduce their usage and reach the ‘signaling’ (i.e. orange) and preferably the ‘target’ (i.e. green) zone (Bos et al., 2013 ; SDa, 2015). These initiatives set very clear targets for the reduction of antimicrobial use in food-producing animals. They do not specify however, how these targets should be best reached, as this question should be addressed at the herd level. The responsibility for reduced antimicrobial use therefore comes down to farmers and their herd veterinarians, reported as being the main advisor with regards to antimicrobial treatments and disease management (Alarcon et al., 2014; Visschers et al., 2015). Similarly for those countries where no benchmarking system is in place, e.g. Belgium and France, herd level action is needed to reduce overall antimicrobial use and achieve national reduction targets.

The question is then the following: how should veterinarians engage farmers to reduce their antimicrobial use and comply with the alternative measures they recommended? The advisory role of the veterinarian needs strengthening, especially in those countries where veterinarians generate a part of their income from selling drugs, but hardly charge for technical advice (Speksnijder et al., 2015b). Strengthened advisory role also implies veterinarians to have better communication skills (Hamood et al., 2014); for example previous research has shown that farmers who understand the logic of the recommended measures and the cause of the disease also better comply with external advice (Alarcon et al., 2014). Veterinary practitioners are still poorly trained in communication, but the situation has been improving in the recent years (Adams and Kurtz, 2006). For example, communication skills were identified as a key component of the OIE guidelines for veterinary education core curriculum (OIE, 2013). Good communication also contributes to the quality of the farmer-veterinarian relationship and especially whether the farmer trusts his/her veterinarian.

Several tools have been developed in human medicine to assess the level of ‘trust in physician’ (Müller et al., 2014); these are scales, generally built on a combination of scores, assessing for example the perceived physician’s level of competencies, attention for the patient or integrity. To our knowledge, such tools are not available in veterinary medicine, but would certainly help to assess the quality of the farmer-veterinarian relationship using a structured and objective approach.

Veterinarians should also be able to adjust their advices to the attitudes of the farmers. Stress was shown to significantly influence farmer’s decision making (Willock et al., 1999), and risk averse farmers are less likely to be willing to implement new measures or to change their practices (Kristensen and Jakobsen, 2011). They are also more likely to reintroduce antimicrobial treatments as soon as clinical signs re-occur. Showing examples of other farms where the implementation of new or alternative measures was successful has been reported as an effective way to convince farmers to change their practices (Alarcon et al., 2014). Exchange of experience with peers and other advisors should therefore be encouraged, but these should not lead to contradictory advice, which were reported as a barrier not to implement veterinary advices, especially in intensive farming (Speksnijder et al., 2015b). The sense of pride of being a good, responsible farmer and importance of the image given to the consumers and the general public were also reported as influencing farmers’ practices in relation with disease control and antimicrobial use, and could be further emphasized by farmer advisors (Green et al., 2010; Alarcon et al., 2014). These findings should be strategically used to form effective communication and policy to motivate farmers and to increase their general engagement.

6.4 Perspectives on the reduction of antimicrobial use in food-producing animals

6.4.1 How far can we reduce AMU in food-producing animals

While an increasing number of initiatives has been implemented to reduce antimicrobial use in food-producing animals, one may wonder how far the use of antimicrobials in food-producing animals should be reduced. Since the early ban on growth-promoting antimicrobials in Sweden in 1986, concerns have been raised about the potential consequences from the reduction of antimicrobial use on animal health, welfare and productivity, e.g. increased diarrhea, weight loss and mortality due to *E.coli* and *Lawsonia intracellularis* in early post-weaning pigs (Casewell et al., 2003). More recently, an association was observed in Danish pigs between the implementation of the 'Yellow card' initiative and a short-term increase in the prevalence of specific lesions found during meat inspection, including chronic peritonitis, umbilical hernia and chronic enteritis (Alban et al., 2013). Although an increase in the therapeutic use of antimicrobials was observed in pigs in Sweden during a 4-year period following the ban on growth-promoting antimicrobials, thereafter the use of antimicrobials decreased because of improved management and addition of zinc oxide to the feed (Wierup, 2001); similar observations were made in Denmark and Norway (Grave et al., 2006). In a recent position paper, the Federation of Veterinarians of Europe re-affirmed that there is no conflict between the responsible and prudent use of antibiotics and good animal welfare; the reduction of antibiotics should be achieved by reducing the need for antimicrobials, rather than by reducing the amount or duration of necessary antimicrobial treatments of properly diagnosed bacterial infections (Federation of Veterinarians of Europe, 2016).

An increasing societal demand for the production of 'pigs raised without antimicrobials' has been noted in several countries. The industry already started responding to this demand and 'antibiotic-free' pork products are being put on the market. Some processors are offering an economic incentive to farmers to raise pigs without antimicrobials in the hopes of filling this demand. Further work is needed to assess the consumers' willingness to pay for these products and establish a transparent certification scheme. The American Association of Swine Veterinarians also stressed the importance for formers involved in the production of pigs raised without antimicrobials to have an alternative marketing plan in place for pigs that still need to be treated with antimicrobials; indeed, it is very clear that animal welfare needs to be assured and that sick pigs need to be treated (American Association of Swine Veterinarians, 2016).

6.4.2 What public health benefit to expect from the reduction of antimicrobial usage in food-producing animals

The ultimate question remains: Which public health benefits can be expected from the reduction of antimicrobial use in food-producing animals? The reversibility of AMR is highly variable and mostly influenced by the fitness cost of resistance, i.e. how the acquisition of resistance genes by a bacterium influences its capability to survive and reproduce. Resistance mechanisms that come with a higher fitness cost are more likely to be reversible, as a reduction in antimicrobial use would benefit the fitter susceptible bacteria, enabling them to outcompete resistant strains over time (Andersson and Hughes, 2010).

In the Netherlands, the use of veterinary antimicrobials was reduced by 50% between 2009 and 2013, following the implementation of a strict policy with defined reduction targets (SDa, 2015); a recent study was conducted to quantify the impact such a reduction had on resistance levels in commensal indicator *E. coli* in animals (Dorado-García et al., 2016). The results showed that the reduction of antimicrobial use in animals led to a significant decrease in *E. coli* resistance in the pig and veal calf production sectors while the impact on the dairy cattle and poultry sectors was less clear. For example, a 54% reduction in total use of antimicrobials in pigs led to a 22% reduction in the pig prevalence of resistance to one or more antimicrobial classes, whereas a 57% reduction in total use of antimicrobials in broilers led to a 8% reduction in the broiler prevalence of resistance to one or more antimicrobial classes. Additionally, resistance levels were more often associated with total antimicrobial use than with class-specific use, suggesting that co-selection of resistance plays an important role in the perpetuation of resistance (Dorado-García et al., 2016). The Netherlands Veterinary Medicines Authority therefore concluded that a reduction in antimicrobial use was likely to further decrease the prevalence of AMR, but the lack of strength and specificity of the observed associations showed it was not relevant, at this stage, to define benchmarking thresholds between farms based on AMR prevalence data (SDa, 2016).

Similar evidence of the impact of changed antimicrobial usage policy is still missing from most countries. Major efforts are therefore needed in the coming decade to document the effect of the current measures. Additionally, because the contribution of the livestock sector to the human burden of AMR is still unknown, it is currently not possible to define an ‘acceptable resistance level’ in animals (SDa, 2016).

6.4.3 How to promote the reduction of antimicrobial usage in animals beyond Europe

While Europe has strongly engaged in the reduction of antimicrobial usage in food-producing animals, and taken the lead in the promotion of the responsible use of veterinary antimicrobials, one should remember that AMR is a global and transboundary threat. It means that for European initiatives to tackle AMR to be effective, other countries should also engage towards the reduction of antimicrobial use. Accurate data on global antimicrobial use in animals are seriously lacking, but recent predictions on the likely growth of antimicrobial use worldwide are quite alarming. Van Boeckel et al. (2015) projected that global antimicrobial use in livestock could rise by 67% between 2010 and 2030, and nearly double in Brazil, Russia, India, China, and South Africa, as a result of the growing consumer demand for livestock products in middle-income countries and a shift to large-scale farming with routine use of antimicrobials.

International organizations have clearly identified the fight against AMR as a key priority for the coming years (FAO/OIE/WHO, 2011) and the reduction of antimicrobial use in food-producing animals is one of the main goals of the Global Action Plan on AMR (World Health Organization, 2015). A number of initiatives to monitor and reduce antimicrobial use in animals have also been implemented worldwide, including in developing countries, e.g. Kenya (Kariuki, 2011) or the Philippines (Philippine Inter-agency Committee on Antimicrobial Resistance, 2016). However, much more has to be done to develop solutions at a global scale (Laxminarayan et al., 2013); the prudent use of antimicrobials should definitely be encouraged via international collaboration (Earnshaw et al., 2013). However, the need to balance the tangible challenge of food security against the more remote risk of antimicrobial resistance may be difficult to overcome.

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Few words on the author

Lucie Collineau was born on the 18th of August 1986 in Mâcon, France. She obtained her Doctor of Veterinary Medicine degree (DVM) in 2012 from the Ecole Nationale Vétérinaire de Toulouse, France. She realised various volunteer project works in international institutions, where she developed strong interest in veterinary public health and international collaboration.

She completed her veterinary curriculum with a MSc in Animal Health and Epidemiology in Southern countries within the French Agricultural Research Centre for Development (CIRAD) in Montpellier, France. Her MSc thesis project focused on the qualitative modelling of animal health surveillance and control systems, and more especially its application to HPAI H5N1 in South East Asia.

In January 2013, Lucie joined SAFOSO as a resident of the European College of Veterinary Public Health (ECVPH). SAFOSO is a Swiss consultancy company with core expertise in animal health and food safety (www.safoso.com). As a resident, she was involved in a diversity of research, consultancy and capacity-building projects, the main one being the MINAPIG project "Minimization of antimicrobial use in pig production", which formed the basis of this PhD thesis. In September 2013, Lucie registered as a PhD candidate at Oniris - Atlantic College of Veterinary Medicine, Food Science and Engineering of Nantes, France. This PhD was therefore conducted in co-supervision between SAFOSO and Oniris.

Lucie especially enjoys bringing together various disciplines, such as epidemiology, economy and social sciences in order to improve animal health and especially livestock production.

APPENDICES

Appendix S1. Indicators of human and animal antimicrobial usage calculated from sales, deliveries and reimbursement data

Table 14. Indicators of human and animal antimicrobial usage calculated from sales, deliveries and reimbursement data

	In words	[Technical unit of measurement] / [Population at risk of being treated]	Period at risk of being treated	Reference [a]
Treatment cost/kg carcass	Antimicrobial treatment cost per kilogram of pig carcass produced	[Total antimicrobial expenditures] / [Annual weight of carcass produced]	1 year (from January to December)	Corrégé et al., 2014
PID	Number of packages per 1000 inhabitants per day	[Number of packages daily reimbursed] / [Number of inhabitants] x 1000	1 year (from July to June)	Coenen et al., 2014
PIID	Number of packages per 1000 insured individuals per day	[Number of packages daily reimbursed] / [Number of insured individuals] x 1000	1 year (from July to June)	Coenen et al., 2014
PCD	Number of packages per 1000 physician contacts per day	[Number of packages daily reimbursed] / [Number of physician contacts] x 1000	1 year (from July to June)	Coenen et al., 2014
Items/1000/day	Number of items per 1000 population per day	[Number of items prescribed] / [Number of inhabitants] x 1000	2 year-period	Scottish Antimicrobial Prescribing Group, 2014
Amount of active substance/PCU	Amount of active substance per Population Correction Unit	[Total amount of active substance sold] / [Number of live and slaughtered animals x standard weight at treatment]	1 year (from January to December)	European Medicines Agency, 2014
Amount of active substance/1000 animals/year	Amount of active substance per 1000 animals and per year	[Total amount of active substance sold] / [Number of animals produced or as livestock] x 1000	1 year (from January to December)	European Medicines Agency, 2013
ALEA (Animal Level of Exposure to Antimicrobials)	Percentage of the animal biomass exposed to antimicrobials	[Total amount of active substance sold / (DDDvet x treatment length)] / [Number of live and slaughtered animals x Standard weight of adults and slaughtered animals]	1 year (from January to December)	Anses, 2014

DDD/1000 inhabitants/year	Number of DDD per 1000 inhabitants and per year	[Total amount of active substance sold / DDD] / [Number of inhabitants] x 1000	1 year (from January to December)	World Health Organization, 2015a
DDD/FCE	Number of DDD per Finished Consultant Episode	[Total amount of active substance sold / DDD] / [Number of finished consultant episodes]	1 year (from January to December)	Curtis et al., 2004
DDDvet/1000 animals/year	Number of DDDvet per 1000 animals and per year	[Total amount of active substance sold / DDDvet] / [Number of animals produced or as livestock x Standard weight at treatment] x 1000	1 year (from January to December)	European Medicines Agency, 2013
nDDay	Number of DDDvet per animal and per year	[Total amount of active substance sold / DDDvet] / [Number of live and slaughtered animals x Standard weight at treatment]	1 year (from January to December)	NETHMAP and MARAN, 2013
TID	Number of treatments per 1000 inhabitants per day	[Number of treatments daily prescribed] / [Number of inhabitants] x 1000	1 year (from July to June)	Coenen et al., 2014
TIID	Number of treatments per 1000 insured individuals per day	[Number of treatments daily prescribed] / [Number of insured individuals] x 1000	1 year (from July to June)	Coenen et al., 2014
TCD	Number of treatments per 1000 physician contacts per day	[Number of treatments daily prescribed] / [Number of physician contacts] x 1000	1 year (from July to June)	Coenen et al., 2014
DCDvet/1000 animals/year	Number of DCDvet per 1000 animals and per year	[Total amount of active substance sold / (DDDvet x Treatment length)] / [Number of animals produced or as livestock x Standard weight at treatment] x 1000	1 year (from January to December)	European Medicines Agency, 2013
DID	Number of DDD per 1000 inhabitants per day	[Number of DDD per day] / [Number of inhabitants] x 1000	1 year (from July to June)	Coenen et al., 2014
DIID	Number of DDD per 1000 insured individuals per day	[Number of DDD per day] / [Number of insured individuals] x 1000	1 year (from July to June)	Coenen et al., 2014
DCD	Number of DDD per 1000 physician contacts per day	[Number of DDD per day] / [Number of physician contacts] x 1000	1 year (from July to June)	Coenen et al., 2014

DDD/100 bed-day	Number of DDD per 100 bed days	[Total amount of active substance sold / (DDD x 365 days)] / [Number of occupied beds] x 100	1 year (from January to December)	World Health Organization, 2015a
DDD/100 admitted patients	Number of DDD per 100 admitted patients	[Total amount of active substance sold / (DDD x 365 days)] / [Number of admitted patients] x 100	1 year (from January to December)	World Health Organization, 2015a
TI_{DDDvet}, TI_{UDDvet} (Treatment incidence)	Number of animals per 1000 receiving a DDDvet or a UDDvet. Also expressed as the percentage of animal life expectancy treated with 1 DDDvet or UDDvet	[Total amount of active substance sold / (DDDvet or UDDvet x Standard weight x production length)] / [Number of animals at risk of being treated] x 1000	1 production period (for growing animals)	Timmerman et al., 2006
DAPD	Proportion (in thousands) of animals treated daily with a DDDvet	[Total amount of active substance sold / (DDDvet x 365 days)] / [Estimated average biomass of the population on any given day] x 1000	1 year (from January to December)	DANMAP, 2013

Indicators are presented here in the same order than in the Figure 5, reading from top to bottom and in case of similar technical units, from left to right.
[a] References accompanying the displayed indicators only provide illustrations of possible applications of the indicators and are not intended to be exhaustive.

Appendix S2. Scatter plots used to select top-farms in Belgium, France and Sweden

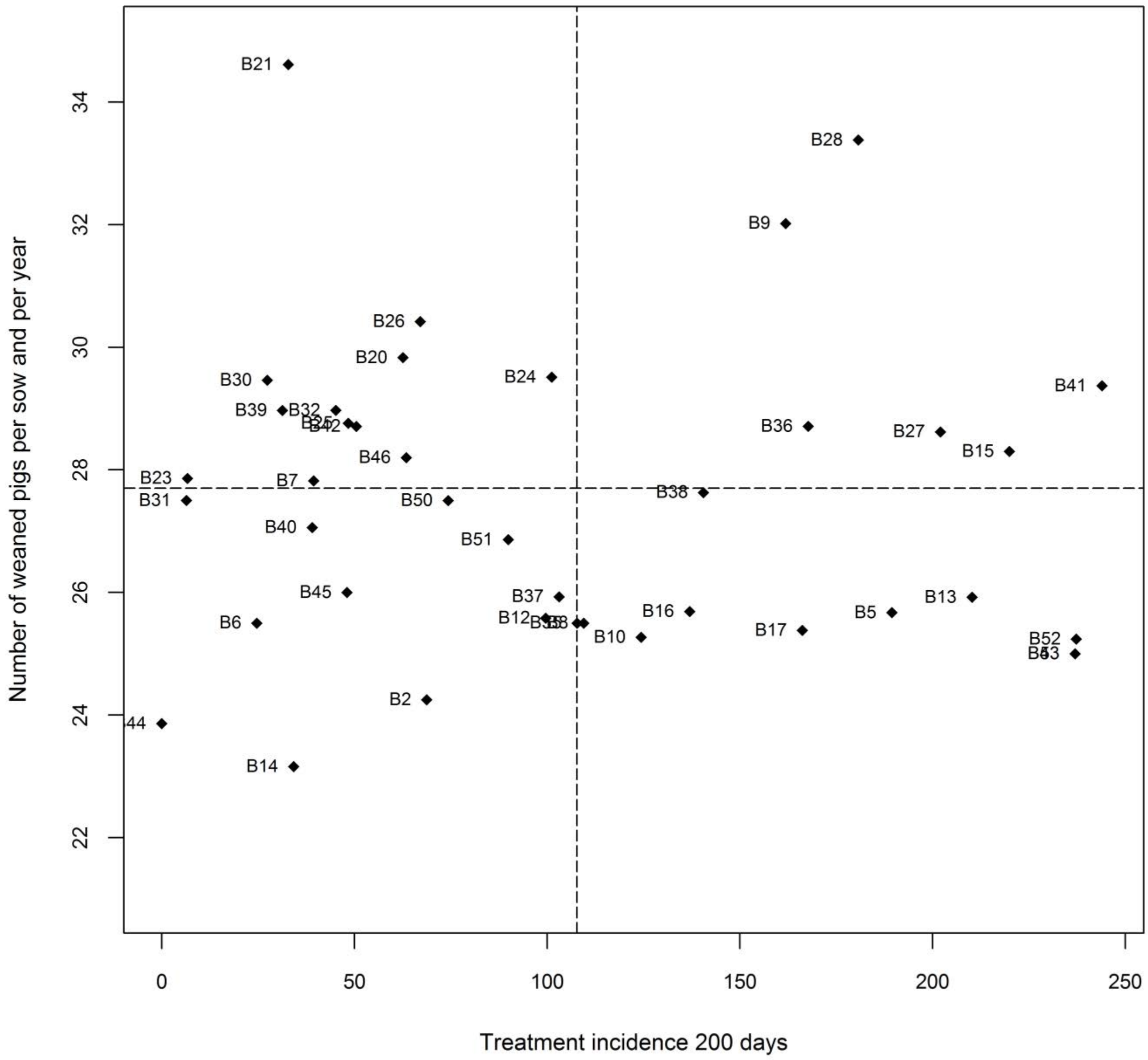

Figure 16. Distribution of the Belgian farms according to their TI200d and their number of weaned pigs per sow and per year

Dotted lines represent the sample median value of the TI200d and the national average of the number of weaned per sow and per year. Farms allocated to the top-farms group were those located in the top left quadrant (excluding those located on the quadrant border).

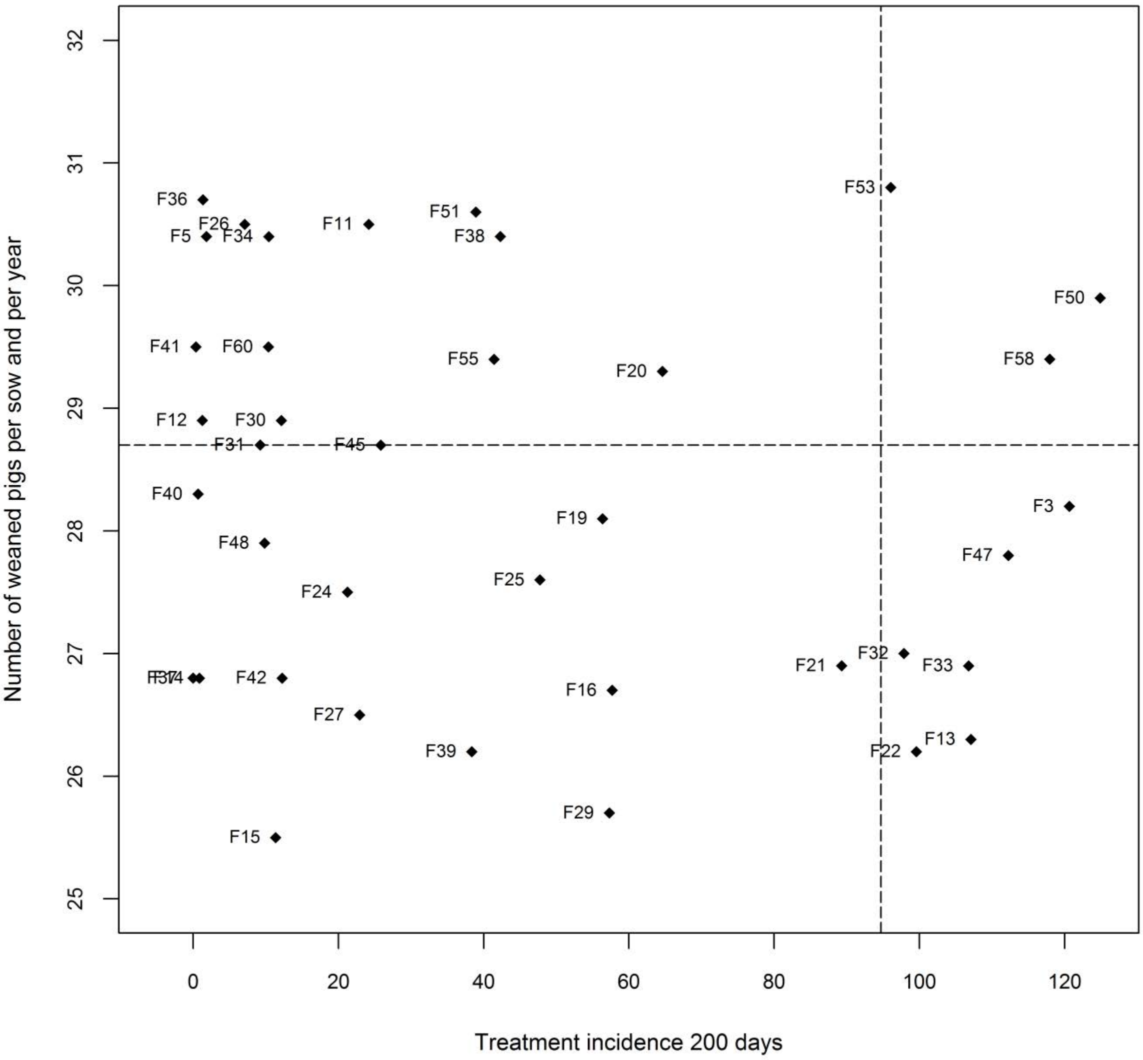

Figure 17. Distribution of the French farms according to their TI200d and their number of weaned pigs per sow and per year

Dotted lines represent the sample median value of the TI200d and the national average of the number of weaned per sow and per year. Farms allocated to the top-farms group were those located in the top left quadrant (excluding those located on the quadrant border).

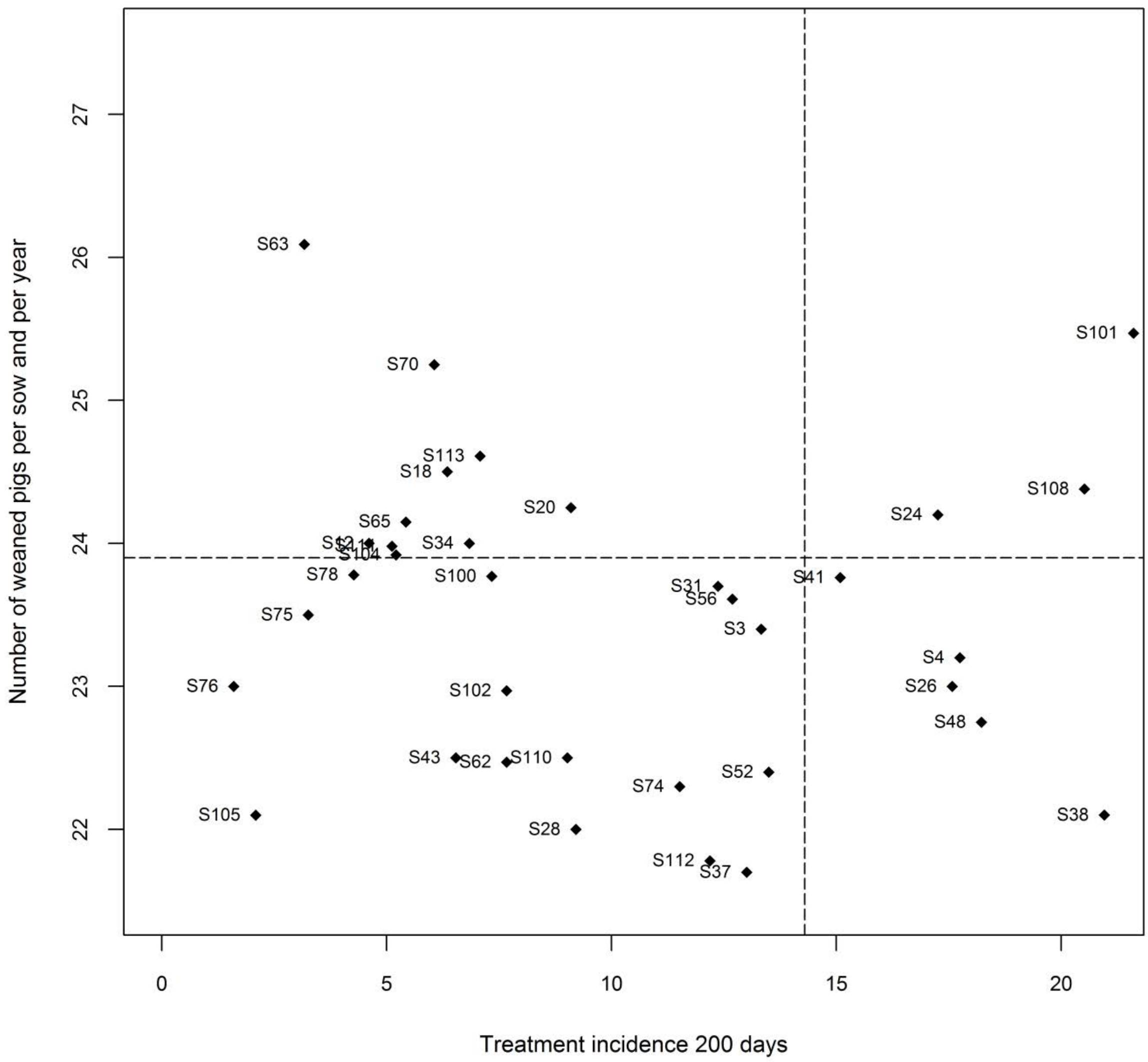

Figure 18. Distribution of the Swedish farms according to their TI200d and their number of weaned pigs per sow and per year

Dotted lines represent the sample median value of the TI200d and the national average of the number of weaned per sow and per year. Farms allocated to the top-farms group were those located in the top left quadrant (excluding those located on the quadrant border).

Appendix S3. Example of report sent to a farmer and a herd veterinarian who participated in the intervention study in France

Intervention report

MINAPIG Project

Project partners

- Project consortium:
- Implementation of French activities :
- Scientific support :

Context and objective

Because of the rising threat from antimicrobial resistance, European countries are working towards the reduction of antimicrobial usage. It requires, among others, reducing antimicrobial usage in livestock production and exploring alternatives to antimicrobial treatments, e.g. reinforced biosecurity or vaccination.

In 2013, 232 pig farms located in four European countries (Belgium, France, Germany and Sweden) participated in a study conducted by the MINAPIG Consortium; it aimed at describing antimicrobial usage and biosecurity practices. Among the 60 French farms that took part to the study, 14 farms with room for improvement to reduce antimicrobial usage accepted to participate in the second part of the study, i.e. an intervention study. Five other volunteer farms also accepted to join the study. Therefore, 19 French farms participated in the intervention study.

You took part, between March 2014 and June 2015, to an intervention study aiming at assessing, from a technical and economic perspective, possible alternatives to antimicrobial usage in pig production. We present here the results of the intervention study conducted at your farm, together with the results obtained in the other French participating farms.

Proposed alternative measures and compliance with the intervention plan

At your farm, it was planned to reduce antimicrobial usage by implementing the following measures:

- Stop the systematic administration of colistin and chlortetracycline via feed (premix) to suckling pigs (used for the prevention of neonatal diarrhea in piglets)
- Stop the systematic administration of colistin and chlortetracycline via feed (premix) to piglets after weaning (used for the prevention of post-weaning diarrhea)
- Stop the administration of tylosin via feed (premix) or water at the beginning of the fattening period (used for the control of porcine ileitis)

Simultaneously were proposed alternative measures aiming at improving pig health at your farm, therefore reducing the need for antimicrobials:

- Implement vaccination of piglets against Porcine circovirus type 2 (PCV2), responsible for post weaning multisystemic wasting syndrome
- Administer homeopathic treatment to sows during the farrowing period

Figures 1 and 2 display the number of systematic treatments that were stopped (Figure 1) and the number of alternative measures that were implemented (Figure 2) as part of the intervention study. Compliance with stopped treatment and alternative measures are also presented. For each treatment that was planned to be stopped, and each measure that was planned to be implemented, a score from 0 (=measure not implemented at all) to 4 (=measure perfectly implemented) was attributed. Scores were then combined into an average compliance score of the farm for treatments to be stopped (Figure 1) and measures to be implemented (Figure 2).

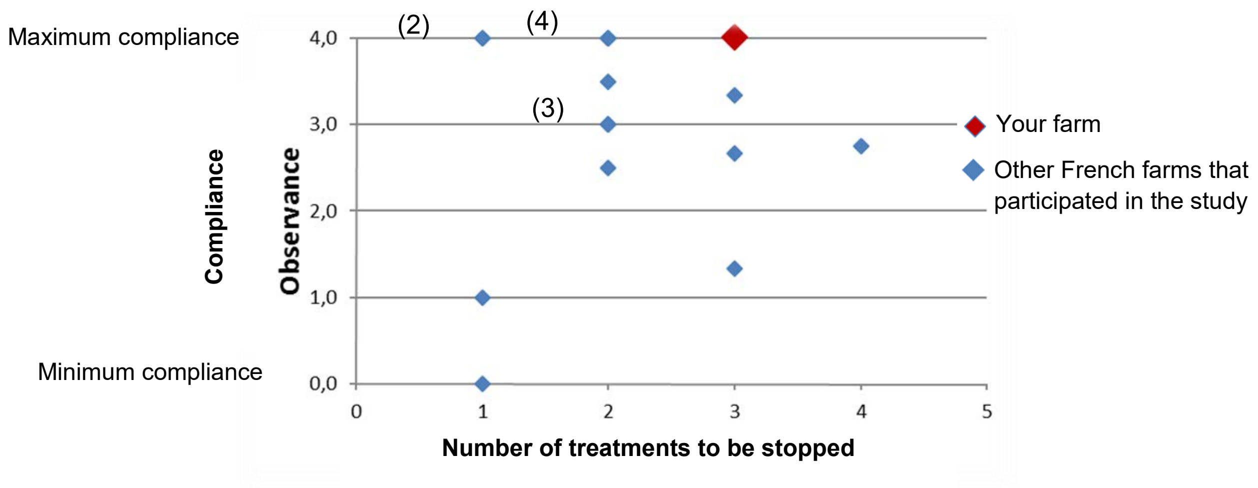

Figure 1. Number of treatments to be stopped in each farm and average compliance score

Figures in brackets indicate the number of overlapping points (i.e. farms with the same number of treatments to be stopped and the same compliance score).

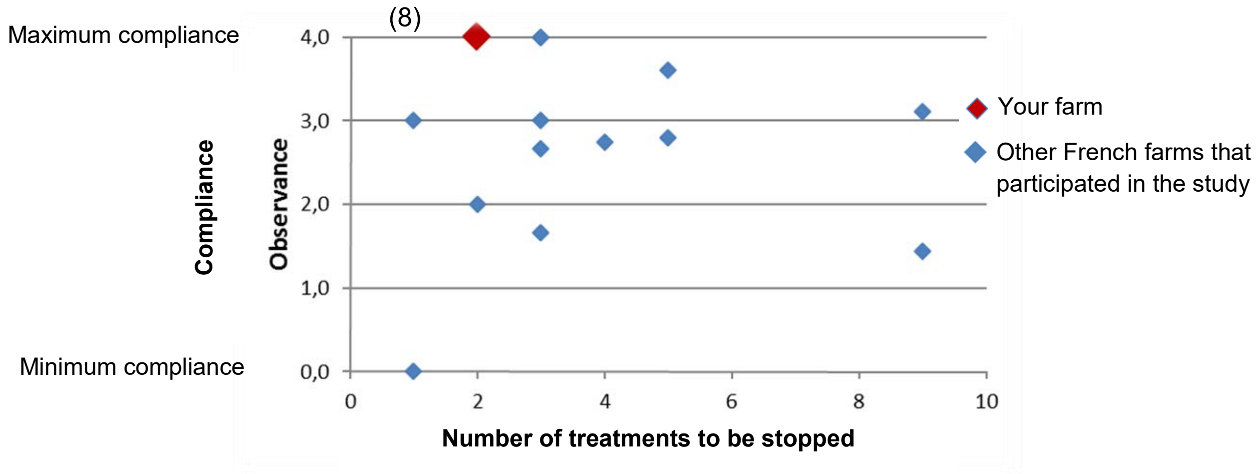

Figure 2. Number of recommended measures in each farm and average compliance score

Figures in brackets indicate the number of overlapping points (i.e. farms with the same number of measures to be implemented and the same compliance score).

As part of the study implemented at your farm, you had three systematic antimicrobial treatments to stop. All of them were stopped as proposed; therefore, you got a score of 4 out 4 for the stopped treatments. Additionally, the two alternative measures that were recommended were perfectly implemented (score of 4 out of 4).

Diminution of antimicrobial usage

The diminution of antimicrobial usage at your farm was estimated by comparing your antimicrobial expenditures during the year 2011 with those from the period between April 2014 and March 2015. Amount of antimicrobials purchased were converted into an indicator called 'treatment incidence', which represents the number of pigs out of 1000 treated with a daily dose of antimicrobials. Treatment incidence was expressed per animal age group and per indication (preventive vs curative), based on the data you reported during the visit at your farm in April 2015. Figure 3 represents the treatment incidences per age group and indication at your farm, both before and after intervention.

About preventive treatments : Since you stopped the administration of antimicrobials in feed to suckling pigs, weaners and fatteners, no more systematic/preventive treatments are administered to your pigs.

About curative treatments: Treatment incidence increased in suckling pigs because you increased your expenditures of parenteral florfenicol (treatment of diarrhea in piglets). In weaners, curative colistin was administered via water (as you stopped the systematic administration in feed). In fatteners, treatment incidence reduced as you stopped the administration of tylosin in feed or water, as well as injections with tiamulin (control of porcine ileitis). In sows, treatment incidence was abnormally high before intervention, because of a sporadic urinary infection that occurred in two batches; these were treated with oxolinic acid in water. No treatments in gilts were reported during the study period.

Economic assessment

Method used for the economic assessment

The economic impact of the intervention implemented at your farm was assessed taking into account four components:

Component 1: the expenses directly related with the intervention; these include potential investments or extra consumables, extra workload, visits of the veterinarian of the technical advisor (the associated costs were estimated using a standard rate for each visit related with the implementation of the follow up of the intervention)

Component 2: any potential savings related with the intervention, in case some activities were stopped as part of the intervention (e.g. in case a vaccination was stopped following the implementation of a new measure, the associated costs were deducted from the cost of the intervention)

Component 3: the variation of the farm standardised economic margin, which accounts for the benefits from the sale of pig carcasses minus the costs of the feed for sows, piglets, and finishers and minus the replacement costs. This indicator was estimated using the PIGSIM tool that was recently developed by the French Pig and Pork Institute (IFIP) and Merial company (the open access tool is available at pigsim.com). Input data were obtained from your farm management systems, i.e. the technical and economical database (GTE) and the sow herd management database (GTTT); the period 2011-2012 (before intervention) was compared with the period 2014-2015 (during intervention)

Component 4: variation of the antimicrobial expenditures at your farm in 2011-2012 compared with 2014-2015.

In order to assess the economic impact of the intervention independently from any potential changes in the pig and feed prices during the observation period, fattening pig and sow prices, as well as feed prices were fixed using the average pig and feed prices in 2014 (source: French Pig and Pork Institute).

The overall economic impact of the intervention at your farm was then evaluated using a so-called ‘partial budgeting’ approach that combined the four components mentioned above. Partial budgeting calculates the difference between the benefits and costs of the intervention.

Benefits include:
- any potential savings associated with the intervention (component 2)
- any potential increase in the farm standardised economic margin (component 3)
- any savings from the reduction of antimicrobial expenditures (component 4)

Costs include:

- direct expenses associated with the intervention (component 1)
- any potential decrease in the farm standardised economic margin (component 3)

Results of the economic assessment performed at your farm

Figure 4 shows the economic impact of the intervention at your farm. The distribution of the results of other participating farms is also displayed. Implemented measures varied a lot from one herd to another: some herds had a lot of measures to implement, with a diversity of associated costs. Your situation compared with other herds is just an indication and should not be interpreted as a success or a failure of the intervention.

To facilitate interpretation of the results in the Figure 4, negative numbers represent losses and positive numbers represent gains.

Expenses directly related with the intervention implemented at your farm were estimated to be 38.00 €/sow/year. They mostly related with the costs of the vaccine against PCV2. You did not report any activity you stopped as part of the intervention (component 2). The standardised economic margin at your farm increased by 148 €/sow/year; it mostly related to an increase in the number of weaned pigs per litter (from 10.7 to 11.5), from a decrease of the mortality rate in fatteners (from 2.1% to 1.1%) and from an increase in the percentage of pigs within the optimum deadweight range (from 78% to 85.6%). In addition, your antimicrobial expenditures decreased by 27.36 €/sow/year. Consequently, the intervention implemented at your farm was associated with an increase in the farm profit estimated to be 137.36 €/sow/year.

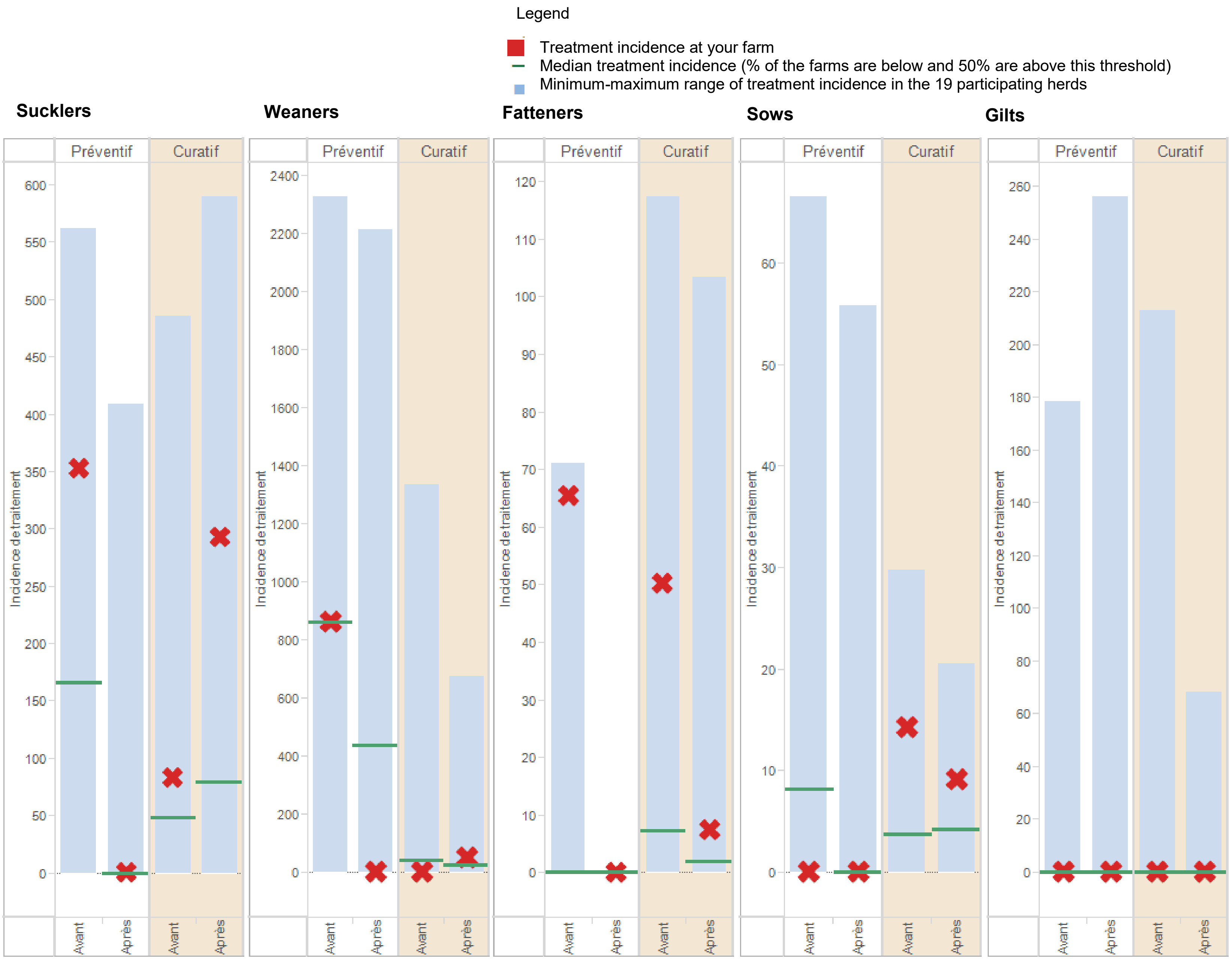

Figure 3. Comparison of treatment incidence before and after intervention, for each age group and preventive/curative indication

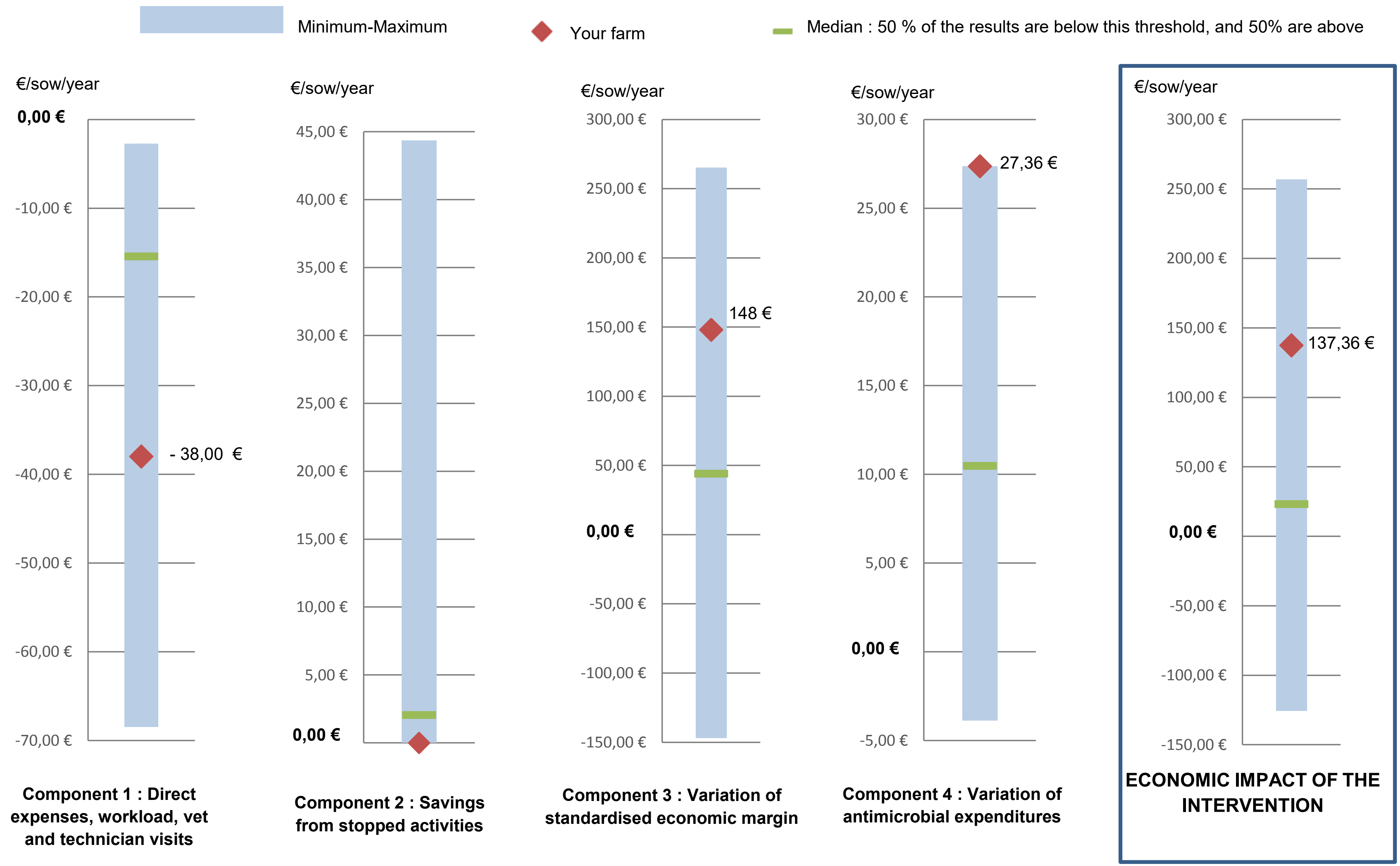

Figure 4 : Assessment of the economic impact of the intervention

The economic impact of the intervention is obtained by summing up the variations observed for the components 1 to 4.

Changes in pig health

Before the intervention, common pig health problems at your farm were neonatal diarrhea and porcine ileitis in fatteners. Following the implementation of PCV2 vaccination and homeopathic treatment to piglets few days after farrowing, the gastro-intestinal health of your pigs substantially improved. Against neonatal diarrhea, you also tried to administer probiotics to piglets after farrowing, but the oral paste was not convenient to administrate. In sucklers, grinding instead of clipping teeth reduced the number of arthritis cases (subsequent infections). In sows, homeopathic treatment around farrowing improved their well-being.

Conclusion

The reduction of antimicrobial usage and the implementation of alternative measures at your farm has been a continuous effort for several years. A substantial reduction of antimicrobial usage was achieved; the vaccination against PCV2 improved the health of growing pig and the homeopathic treatment had a positive effect on sows around farrowing. The intervention was relatively expensive compared with other herds, but simultaneously, the standardised economic margin significantly increased and your antimicrobial expenditures decreased; overall, the intervention implemented at your farm was successful.

Thank you very much for your participation to the study

For your information, a similar study was implemented in 14 farms in Belgium, 25 farms in Germany and 9 farms in Sweden. Data are currently being analysed and results will be disseminated soon.

For any question or comment related to this report or to the MINAPIG study, please feel free to contact us at the following address:

Lucie Collineau, lucie.collineau@safoso.ch, tel : 0041 31 544 25 04

Catherine Belloc, catherine.belloc@oniris-nantes.fr, tel: 02 40 68 77 91

Appendix S4. Input data used as part of the cost accounting analysis performed to quantify the direct net costs of the interventions

Table 15. Price and expected duration of equipment or single expenses

Item	Median price (€ per unit, excluding VAT)	Expected duration (years)	Source
Annual rent for an extra building to accommodate 27 sows	2971.47	1	Farmer
Automatic syringe	47.58	2	http://lecarrefarago.com www.vital-concept-agriculture.com www.calipro.fr
Basket for split suckling management	15.00	2	Farmer
Boot washer	270.00	4	http://lecarrefarago.com
Boots	36.00	1	www.agrodirect.fr www.vital-concept-agriculture.com www.calipro.fr
Equipment for water treatment with salt water electrolyte solution	32532.00	5	Farmer
Feed trough	50.00	5	Farmer
Gas mask for safety when disinfection	80.00	3	Farmer
Inleds air change	204.75	10	Farmer
New quarantine building for gilts (in a 200-sow farm)	30000.00	15	Farmer
Overalls	34.00	1	www.agrodirect.fr www.vital-concept-agriculture.com
Renovation of weaners building (in a 190-sow farm)	25000.00	10	Farmer
Serological analysis	8.87	1	www.labocea.fr
Thermometer	4.00	2	Farmer
Ventilators change	4500.00	10	Farmer
Water chemical and physical analysis (pH, hardness, NO3, NH4, Mn, Fe)	10.92	1	www.labocea.fr
Water pump	800.00	3	Farmer

Table 16. Price of vaccine doses and other consumables

Item	Unit	Median price (€ per unit, excluding VAT)	Source
Vaccine doses			
Escherichia coli vaccine	dose	0.71	www.centravet.fr www.alcyon.com
Escherichia coli + *Clostridium spp.* vaccine	dose	1.67	
Shigatoxin Stx2e-producing *Escherichia coli* vaccine	dose	1.66	
Lawsonia intracellularis vaccine	dose	1.25	
Porcine Respiratory and Reproductive Syndrome Virus vaccine	dose	1.38	
Actinobacillus pleuropneumoniae vaccine	dose	0.82	
Porcine influenza virus vaccine	dose	1.46	
Atrophic rhinitis vaccine	dose	2.81	
Mycoplasma hyopneumoniae vaccine	dose	0.61	
Porcine circovirus 2 vaccine	dose	1.23	
Haemophilus parasuis vaccine	dose	0.87	
Autogenous vaccine in sows	dose	1.57	http://vaccines.biovac.fr/en/ www.filavie.fr/ www.labocea.fr
Autogenous vaccine in piglets	dose	0.57	
GnRH vaccination for piglet castration (Improvac®)	dose	1.43	Farmer
Other consumables			
Animal disinfectant product (e.g. Povidone-iodine)	euros per liter	6.71	www.agrodirect.fr www.vital-concept-agriculture.com www.calipro.fr
Disposable gloves	box of 100	6.9	
Castration blades	box of 5	0.89	
Scalpel handle	unit	1.75	
Injection Needles	box of 100	5.21	
Vaccination needles	unit	0.15	
Rodent elimination visit	visit	150	http://farago-bretagne.fr
Oral iron supplementation (e.g. VeyFo® Tan-O-Lin HFH DUO-Min)	euros per kg of product	8.50	https://www.veyx.de/

Maintenance of equipment for water treatment with salt water electrolyte solution	euros per m3	0.05	www.ocene.fr
Maintenance cost of water treatment with hydrogen peroxide	euros per m3 of water	0.03	www.agrodirect.fr www.vital-concept-agriculture.com
Maintenance water chlorination	euros per m3	0.05	www.calipro.fr www.ocene.fr

For other consumable products including feed additives, phyto-therapeutical, anti-inflammatory and deworming products, cleaning and disinfection products, exact prices were provided by the farmer for each particular product.

Appendix S5. Antimicrobial prices per administration route and active substance

Table 17. Antimicrobial prices per administration route and active substance

Administration route	Active substance	Average price (€ per gram of active substance)
Feed	Amoxicillin	0.12
	Apramycin	0.55
	Apramycin + Colistin	0.31
	Benzylpenicillin	0.12
	Chlortetracyclin	0.05
	Chlortetracyclin + Colistin	0.07
	Colistin	0.08
	Lincomycin + Spectinomycin	1.18
	Lincomycin + Spectinomycin + Colistin	0.55
	Oxytetracyclin	0.03
	Oxytetracyclin + Colistin	0.04
	Thrimethoprim + Sulfadiazin	0.03
	Thrimethoprim + Sulfadimethoxin	0.03
	Tiamulin	0.51
	Tilmicosin	0.31
	Tylosin	0.19
Oral	Apramycin	0.25
	Colistin	107.86
	Colistin + Sulfaguanidin	14.11
	Enrofloxacin	5.72
	Oxolinic acid	2.77
	Spectinomycin	2.52
	Tiamulin	0.69
Parenteral	Amoxicillin	3.11
	Amoxicillin LA [a]	1.45
	Ampicillin	1.60
	Ampicillin LA	2.02
	Benzylpenicillin	0.30
	Benzylpenicillin + Dihydrostreptomycin	0.26
	Benzylpenicillin LA	0.45
	Benzylpenicillin LA + Dihydrostreptomycin	0.60
	Cefquinom	18.44
	Ceftiofur	11.71
	Ceftiofur LA	14.42
	Colistimethate + Benzylpenicillin	0.59
	Colistin	2.52
	Colistin + Amoxicillin	2.60
	Colistin + Ampicillin	0.95
	Danofloxacin	17.81
	Enrofloxacin	5.72
	Enrofloxacin LA	5.72
	Erythromycin	1.78
	Florfenicol LA	1.25
	Gentamycin	1.80
	Lincomycin	1.36
	Lincomycin + Spectinomycine	1.65
	Marbofloxacin	7.20
	Oxytetracyclin	1.58

	Oxytetracyclin LA	0.82
	Paromomycin	1.27
	Spectinomycin	1.28
	Spiramycin	1.00
	Sulfadimethoxin	0.34
	Sulfadimidin	0.34
	Sulfamethoxypyridazin	0.34
	Thrimethoprime + Sulfadiazin	1.00
	Thrimethoprime + Sulfadimethoxin	0.41
	Thrimethoprime + Sulfadoxin	0.91
	Thrimethoprime + Sulfamethoxypyridazin	0.43
	Tiamulin	1.64
	Tildipirosin	13.04
	Tulathromycin LA	22.88
	Tylosin	1.05
	Tylosin LA	1.05
Topical	Chlortetracyclin	3.42
	Chlortetracyclin + Sulfanilamid	0.07
	Oxytetracyclin	0.57
	Thiamphenicol	1.42
Water	Amoxicillin	0.08
	Ampicillin	0.29
	Ampicillin + Sulfadimethoxin	1.33
	Apramycin	0.75
	Chlortetracyclin + Sulfamethoxypyridazin	0.14
	Colistin	0.19
	Colistin + Erythromycin	3.66
	Colistin + Neomycin	0.28
	Colistin + Thrimethoprim	0.42
	Dihydrostreptomycin	0.26
	Doxycyclin	0.13
	Florfenicol	0.68
	Flumequin	0.13
	Lincomycin	0.62
	Lincomycin + Spectinomycine	0.52
	Neomycin	0.11
	Oxolinic acid	0.39
	Oxytetracyclin	0.08
	Oxytetracyclin + Neomycin	0.10
	Oxytetracyclin + Spiramycin	0.33
	Spiramycin	0.38
	Sulfadimethoxin	0.12
	Sulfadimidin	0.03
	Sulfaguanidin	0.12
	Sulfaguanidin + Sulfadimidin	0.17
	Tetracyclin	0.05
	Thrimethoprim + Spiramycin	0.37
	Thrimethoprim + Sulfadiazin	0.15
	Thrimethoprim + Sulfadimethoxin	0.16
	Thrimethoprim + Sulfamethoxypyridazin	0.21
	Tiamulin	0.49
	Tilmicosin	0.36
	Tylosin	0.19
	Tylvalosin	0.54

[a] LA = long acting product

Source: An initial list of prices was prepared using for each combination of administration route/active substance, the average antimicrobial price across commercial products, product compositions (i.e. amount of active substance per amount of product) and package sizes, as provided by the two main veterinary antimicrobial retailers in France (http://www.alcyon.com ; http://www.centravet.fr/). MINAPIG Consortium partners reviewed the initial list and provided input on combinations of administration route/active substance not authorized in France. Minor changes were then performed after review of the list by a French pig veterinarian practitioner, and using input from Rojo-Gimeno et al. (2016).

Reference

Rojo-Gimeno, C., Postma, M., Dewulf, J., Hogeveen, H., Lauwers, L., Wauters, E., 2016. Farm-economic analysis of reducing antimicrobial use whilst adopting improved management strategies on farrow-to-finish pig farms. Prev. Vet. Med. 129, 74–87. doi:10.1016/j.prevetmed.2016.05.001

Appendix S6. Definition of the Belgian and French reference farrow-to-finish farms used in the input-output production economic model

(adapted from Rojo-Gimeno et al. (2016))

Table 18. Definition of the Belgian and French reference farrow-to-finish farms used in the input-output production economic model

	French reference farm	Source	Belgium reference farm	Source
Finishing phase				
Weight of the piglets at the beginning of the finishing period (kg)	31.6	IFIP 2014	22.4	FADN 2010-2012
Feed prices for finishers (€ /kg)	0.25	AHDB, 2016	0.26	
Finishing pigs' final weight (kg)	117	IFIP 2014	111	
Average number of present finishing pigs	1608	Estimated[a]	1057	
Prices for kg of living weight of the finishers (€ /kg)	1.45	IFIP 2014	1.19	
Mortality in the finishing period (%)	3.6	IFIP 2014	3.0	
Average daily weight gain during the finishing period (g/day)	748	IFIP 2014	644	
Feed conversion ratio during the finishing period (kg feed/kg meat)	2.96	IFIP 2014	2.93	
Farrowing phase				
Feed prices for sows and gilts (€/kg)	0.27	AHDB, 2016	0.25	FADN 2010-2012
Feed prices for piglets (€ /kg)	0.37	AHDB, 2016	0.38	
Average number of present gilts	20	IFIP 2014	13	
Average number of present sows	212	IFIP 2014	144	
Average number of present piglets	1252	Estimated[a]	685	
Weaning age (days)	23.6	AHDB, 2016	25.8	
Litter size (i.e. number of piglets born alive per litter)	13.4	IFIP 2014	11.1	
Farrowing index (i.e. number of farrowings per sow per year)	2.35	AHDB, 2016	2.25	
Mortality of piglets (i.e. mortality in maternity and nursery) (%)	16.2	IFIP 2014	12.8	

[a] The average numbers of present piglets and present finishing pigs are not normally recorded in the French technical management systems; these were estimated assuming a 3-week farrowing system, which is the most commonly used in France (IFIP 2014).

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Appendix S7. Correlation of pig and feed prices in Belgium and France

Table 19. Correlation matrix of the prices of finishers (PYF) and piglets (PYP) and feed prices of finishers (PFF), sows (PFS) and piglets (PFP) in Belgium (adapted from (Rojo-Gimeno et al., 2016))

	PY_F[a]	PY_P[b]	PF_F[c]	PF_S[d]	PF_P[d]
PY_F[a]	1.00	0.68	0.54	0.53	0.54
PY_P[b]	0.68	1.00	0.00	0.00	0.00
PF_F[c]	0.54	0.00	1.00	1.00	1.00
PF_S[d]	0.53	0.00	1.00	1.00	1.00
PF_P[d]	0.54	0.00	1.00	1.00	1.00

[a] Prices of finishers
[b] Prices of piglets
[b] Feed prices of finishers
[c] Feed prices of sows
[e] Feed prices of piglets
Source: feed prices were estimated using monthly data from the Flemish government (Department of Agriculture and Fisheries, Flemish Government) and pig prices from a Belgian feed company (Vanden Avenne) for the years 2010, 2011 and 2012

Table 20. Correlation matrix of the prices of finishers (PYF) and piglets (PYP) and feed prices of finishers (PFF), sows (PFS) and piglets (PFP) in France

	PF_F[a]	PY_P[b]	PY_F[c]	PF_S[d]	PF_P[e]
PF_F[a]	1.00	0.51	0.69	0.99	0.98
PY_P[b]	0.51	1.00	0.61	0.53	0.59
PY_F[c]	0.69	0.61	1.00	0.66	0.61
PF_S[d]	0.99	0.53	0.66	1.00	0.98
PF_P[e]	0.98	0.59	0.66	0.98	1.00

[a] Prices of finishers
[b] Prices of piglets
[b] Feed prices of finishers
[c] Feed prices of sows
[e] Feed prices of piglets
Source: feed prices were estimated from monthly data from the French National Institute of Statistics and Economic Studies (INSEE) and pig prices from FranceAgriMer for the years 2013, 2014 and 2015

Appendix S8. Detailed fitted distributions for Belgium and French data

Table 21. Detailed fitted distributions of the parameters of the model for Belgium

	Distribution	AIC	Mean	SD	Formulation in @Risk
∆DWG[a]	Normal	-11.3129	0.0059	0.0978	RiskNormal (0.0059052; 0.0097763)
∆AM costs[b]	Pert	137.5783	-26.4105	35.7779	RiskPert (-238.075; 15.9222; 15.9222)
∆FC ratio[c]	Normal	-30.4204	-0.0227	0.0495	RiskNormal (-0.22747; 0.049478)
∆FI[d]	Triangular	-52.3748	-0.0181	0.0263	RiskTriang (-0.055319; -0.055319; 0.056247)
∆Intervention costs[e]	Normal	130.7398	16.8900	16.5390	RiskNormal (16.89; 16.539)
∆LS[f]	Extreme values	-40.1824	0.0512	0.0448	RiskExtValue (0.031027; 0.034965)
∆MF[g]	Extreme value minimum	-63.5973	-0.00922	0.0183	RiskExtValueMin (-0.00098592; 0.014266)
∆M Piglets[h]	Extreme value minimum	31.9222	-0.0104	0.0492	RiskExtValueMIn (0.011757; 0.038371)

[a] difference on daily weight gain; [b] difference in antimicrobial costs; [c] difference in feed conversion ratio; [d] difference in farrowing index; [e] difference in intervention costs; [f] difference in litter size; [g] difference in mortality of the finishers; [h] difference in mortality of the piglets

Table 22. Detailed fitted distributions of the parameters of the model for France

	Distribution	AIC	Mean	SD	Formulation in @Risk
∆DWG[a]	Extreme value	91.21	1.17	3.30	RiskExtvalue (-0.31678; 2.5724)
∆AM costs[b]	Normal	156.71	-9.4343	13.549	RiskNormal (-9.4343; 13.549)
∆FC ratio[c]	Triangular	97.46	-1.07	4.02	RiskTriang (-12.431; 4.6099; 4.6099)
∆FI[d]	Laplace	57.23	0.5844	1.6747	RiskLaplace (0.58442; 1.6747)
∆FW[e]	Extreme value		0.0098	0.020	RiskExtvalue (-0.3781;3087)
∆Intervention costs[f]	Extreme value	175.35	13.64	23.22	RiskExtvalue (3.1932; 18.105)
∆LS[g]	Uniform	72.54	1.11	3.21	RiskUniform (-4.4478; 6.6723)
∆MF[h]	Extreme value	74.95	0.38	1.68	RiskExtvalue (-0.3781; 3087)
∆M Piglets[i]	Exponential	59.35	0.51	2.38	RiskExpon (2.3786; RiskShift (-1.8699))

[a] difference on daily weight gain ; [b] difference in antimicrobial costs; [c] difference in feed conversion ratio; [d] difference in farrowing index; [e] difference in intervention costs; [f] difference in finishing weight; [g] difference in litter size; [h] difference in mortality of the finishers; [i] difference in mortality of the piglets

Appendix S9. Detailed herd-level results of the farm economic analysis

Table 23. Detailed herd-level results of the farm economic analysis performed in a subset of farms (n=33 farms)

Country	Farm ID	Δ Margin over feed cost $_{after-before}$ (€ per sow per year)		Δ Antimicrobial expenditures $_{after-before}$ (€ per sow per year)	Direct net cost of the intervention (€ per sow per year)	Δ Net farm profit $_{after-before}$ (€ per sow per year)	
		Deterministic model	Stochastic model Mean (95% CI)			Deterministic model	Stochastic model Mean (95% CI)
Belgium	B1	-40.40	-39.08 (-55.18; -22.91)	-20.12	42.46	-62.74	-61.42 (-77.52; -45.25)
	B2	28.46	27.57 (10.34; 43.27)	3.02	23.32	2.12	1.23 (-16.00; 16.93)
	B3	10.01	9.27 (-5.31; 22.79)	1.68	13.90	-5.57	-6.31 (-20.89; 7.21)
	B4[a]	5.59	6.01 (-10.99; 25.12)	1.42	-18.39	22.56	22.98 (5.98; 42.09)
	B5	-54.33	-54.16 (-74.52; -33.61)	-5.19	30.74	-79.88	-79.71 (-100.07; -59.16)
	B6	49.23	48.61 (28.91; 68.01)	-2.30	1.64	49.89	49.27 (29.57; 68.67)
	B7	23.20	16.04 (-47.88; 76.81)	-5.77	24.51	4.46	-2.70 (-66.62; 58.07)
	B8	98.98	92.61 (33.26; 150.38)	-8.42	26.57	80.82	74.45 (15.10; 132.22)
	B9	80.42	82.94 (65.53; 100.13)	-72.00	19.29	133.13	135.65 (118.24; 152.84)
	B11	17.04	16.29 (1.90; 29.43)	-155.67	7.61	165.10	164.35 (149.96; 177.49)
	B12[a]	28.39	30.59 (5.39; 57.12)	15.92	16.37	-3.90	-1.70 (-26.90; 24.83)
	B13[a]	89.40	89.58 (69.34; 109.70)	-4.82	23.53	70.69	70.87 (50.63; 90.99)

	B14[a]	113.93	119.36 (81.64; 157.66)	5.35	1.58	107.00	112.43 (74.71; 150.73)
	B16	41.25	42.83 (33.18; 52.69)	3.90	41.48	-4.13	-2.55 (-12.20; 7.31)
France	F1	-113.89	-115.11 (-134.34; -95.81)	-9.36	-9.43	-95.11	-96.33 (-115.56; -77.03)
	F2[a]	-5.23	-5.77 (-7.04; -4.59)	17.78	2.56	-25.58	-26.12 (-27.39; -24.94)
	F3[a]	0.40	0.57 (-3.77; 4.78)	-20.25	8.65	12.00	12.17 (7.83; 16.38)
	F4	54.65	54.78 (44.67; 65.42)	0.38	58.04	-3.78	-3.65 (-13.76; 6.99)
	F5[a]	-32.82	-32.83 (-42.70; -23.62)	-1.51	1.23	-32.54	-32.55 (-42.42; -23.34)
	F6	199.40	201.72 (175.90; 229.86)	-11.79	18.32	192.87	195.19 (169.37; 223.33)
	F7	100.45	100.89 (83.95; 118.41)	-2.85	22.80	80.50	80.94 (64.00; 98.46)
	F8	18.47	18.61 (12.18; 25.08)	-5.64	-16.40	40.51	40.65 (34.22; 47.12)
	F9	-64.78	-65.79 (-73.38; -59.31)	-10.65	-5.18	-48.95	-49.96 (-57.55; -43.48)
	F10[a]	-35.67	-32.61 (-41.07; -31.08)	-19.73	18.24	-34.18	-31.12 (-39.58; -29.59)
	F11	39.61	39.77 (31.44; 48.19)	-29.28	56.36	12.52	12.68 (4.35; 21.10)
	F13	-73.69	-74.49 (-86.67; -62.89)	-35.42	5.17	-43.44	-44.24 (-56.42; -32.64)
	F14	99.07	99.12 (80.84; 118.23)	-19.81	-20.42	139.29	139.34 (121.06; 158.45)
	F15	154.16	155.42 (131.08; 181.02)	-13.33	8.06	159.43	160.69 (136.35; 186.29)
	F16	55.39	56.40 (45.44; 67.56)	-8.82	4.39	59.82	60.83 (49.87; 71.99)

F17	-104.18	-105.25 (-123.02; -87.76)	9.92	2.72	-116.83	-117.90 (-135.67; -100.41)
F18[a]	-22.66	-23.00 (-26.60; -19.63)	-23.18	38.00	-37.48	-37.82 (-41.42; -34.45)
F19[a]	146.34	147.65 (130.62; 166.57)	-4.67	63.55	87.47	88.78 (71.75; 107.70)
F20	7.59	7.90 (4.76; 11.04)	8.95	8.04	-9.40	-9.09 (-12.23; -5.95)
Median farm (Q25 ; Q75)	23.20 (-22.66; 80.42)	18.61 (-23.00; 82.94)	-5.64 (-19.73; 1.42)	13.90 (2.56; 24.51)	4.46 (-32.54; 80.50)	1.23 (-31.12; 74.45)

[a] Margin over feed cost was estimated with the scenario which accounted for a fixed number of sows

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SANTÉ ET ALIMENTATION AU CŒUR DE LA VIE

Thèse de Doctorat

Lucie COLLINEAU

Quantify, Explain and Reduce Antimicrobial Usage in Pig Production in Europe

Quantifier, Comprendre et Réduire l'Utilisation des Antibiotiques en Elevage Porcin en Europe

Abstract

Because of the growing threat from antimicrobial resistance, a number of international, European and national initiatives have been developed to mitigate the risk arising from antimicrobial use in animals. However, these initiatives are facing challenges and information gaps, especially related to how to quantify, explain and reduce antimicrobial use in food-producing animals.

The objective of this PhD thesis was to address some of these challenges, focusing on the pig sector and the herd level, and exploring more specifically i) what are the most suitable indicators that should be selected to quantify antimicrobial use, ii) what is the relative importance of selected technical and psychosocial drivers for antimicrobial use in pig production, iii) what is the profile of pig farms that manage to combine high technical performance and low antimicrobial usage and iv) what is the technical and economic impact of the implementation of alternative measures to reduce antimicrobial use in pig production.

This work contributed to provide a basis for effective, evidence-based yet affordable strategies to mitigate the public health burden of antimicrobial resistance.

Key Words

Antimicrobial use, Antibiotic, Antimicrobial stewardship, Drivers, Intervention study

Résumé

La résistance aux antibiotiques représentant une menace grandissante pour la santé publique, un certain nombre d'initiatives ont été mises en œuvre au niveau international, européen et national, afin de maitriser le risque lié à l'utilisation des antibiotiques en médecine vétérinaire. Ces initiatives se heurtent néanmoins à des difficultés techniques et à un manque de données scientifiques, notamment pour quantifier, comprendre et réduire l'utilisation des antibiotiques en élevage.

L'objectif de ces travaux de thèse était d'aborder certaines de ces difficultés, en travaillant plus particulièrement à l'échelle de l'élevage porcin, afin d'explorer i) quels sont les indicateurs les plus adaptés à la quantification de l'utilisation des antibiotiques, ii) quelle est l'importance relative des principaux déterminants techniques et psychosociologiques de l'utilisation des antibiotiques en élevage porcin, iii) quelles sont les caractéristiques des éleveurs qui combinent à la fois un faible usage en antibiotiques et de bonnes performances techniques, iv) quel est l'impact technique et économique de la mise en œuvre de mesures visant à réduire l'usage des antibiotiques en élevage porcin.

Ces travaux ont contribué à la construction d'une base scientifique pour le développement de stratégies efficaces et accessibles afin de maitriser l'impact de la résistance aux antibiotiques sur la santé publique.

Mots clés

Utilisation des antibiotiques, Bonnes pratiques, Déterminants, Etude d'intervention