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Estimating Average Lifetime Antimicrobial Exposure of Danish Slaughter Pigs in a Fast, Automated and Robust Way

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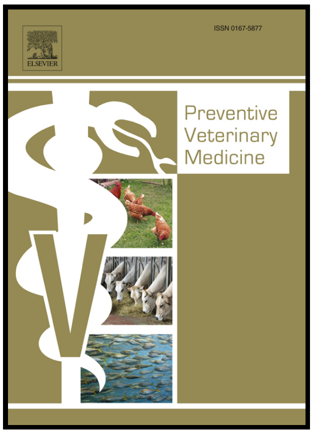

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Calculating and estimating antimicrobial exposure at specific pig level is key to understanding consumption patterns of antimicrobials in the Danish pig sector. Understanding consumption and trading patterns can assist in developing treatment plans at national and local levels to reduce antimicrobial resistance. The ALEX algorithm is a fast, automated and robust algorithm developed to estimate the average lifetime antimicrobial exposure of Danish slaughter pigs. The algorithm estimates antimicrobial exposure in the different life stages of the pig (piglet, weaner and finisher) together with the type of production network. We present the algorithm and give two examples of usage, as well as providing a comparison of the ALEX algorithm with an acknowledged exposure estimation algorithm, and presenting a sensitivity analysis.

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The ALEX Algorithm - Estimating Average Lifetime Antimicrobial Exposure of Danish Slaughter Pigs in a Fast, Automated and Robust Way

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Abstract

Calculating and estimating antimicrobial exposure at specific batch level is key to understanding consumption patterns of antimicrobials in the Danish pig sector. Understanding consumption and trading patterns can assist in developing treatment plans at national levels and might lead to reducing antimicrobial resistance levels. The ALEX algorithm is a fast, automated and robust algorithm developed to estimate the average lifetime antimicrobial exposure of Danish slaughter pigs. The algorithm estimates antimicrobial exposure in the different life stages of the pig (piglet, weaner and finisher) together with the type of production network (the number of farms within a network and ownership of these). We present the algorithm and give two examples of usage. Furthermore, we compare the ALEX algorithm with an acknowledged exposure estimation algorithm, and we present a sensitivity analysis.

Keywords: Antimicrobial exposure, AMU, Average lifetime antimicrobial calculations, Danish pig production, The ALEX algorithm

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1. Introduction

Antimicrobial use (AMU) is known to constitute a risk of spreading antimicrobial resistance (AMR) (Holmes et al., 2016; MacGowan and Macnaughton, 2017). In 2020, two thirds of the total use of antimicrobials in Denmark was prescribed for veterinary use. The Danish pig sector accounted for 76 % of this veterinary antimicrobial consumption, corresponding to 75.9 tonnes active compound (DANMAP, 2021). To monitor the exposure of antimicrobials in livestock at national level, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) was founded in 1995 (DANMAP, 2021). DANMAP reports are based on the Danish national registry for prescriptions for drugs for veterinary use (VETSTAT). While DANMAP reports are important in national monitoring at the animal species level, the average antimicrobial exposure at the pig level can be used to study the association between AMR and AMU (Birkegård et al., 2017). Such estimations allow us to investigate the relationship between AMR measured in sampled pigs and the AMU for the particular pigs in the different age stages, as well as the effect of changing AMU between batches from same farm sampled at different time points on AMR (Andersen et al., 2020; Munk et al., 2017).

Denmark has a well-established pig production industry, 32 million pigs were produced in 2021 (Danish Agriculture and Food Council, 2021). In the production of finishers, the rearing pathway consists of the farrowing section, the weaning section, and the finishing section. Within these three sections, pigs are grouped based on their weight: piglets (up to 7 kg), weaners (7-30 kg) or finishers (over 30 kg). Because of the large pig production in

Denmark, a number of different ways of producing pigs exists depending on the housing system, the type of production and how this is organized i.e. if the pigs stay on the same farm until slaughter or if they are moved to other farms (Christiansen, 2021). Integrated farms include all three rearing groups and pigs therefore stay on the same farm from birth until slaughter. Multi-site productions also include all three rearing groups, but they are situated at two or more geographical locations, although all farms have the same owner. Specialized farms are farms housing only sows and piglets, weaners, or finishers. There are also farms housing a combination of these. This results in many distinct trading and movement patterns between the farms in Denmark (Birkegård et al., 2017; Schulz et al., 2017). The movements of pigs between farms make the estimation of AMU for a specific pig difficult, since neither the movement for the specific pig nor the exposure is registered on an individual level.

Here we introduce a highly effective and robust algorithm to calculate Average Lifetime EXposure (ALEX) for Danish slaughter pigs entirely based on complex register data at farm level. Besides presenting the algorithm, we also demonstrate its utility by describing two uses of the algorithm. A comparison with a similar existing algorithm (a lifetime exposure to antimicrobial algorithm - the LEA algorithm (Birkegård et al., 2017)) is carried out and a sensitivity analysis of selected parameters is included.

2. Materials and methods

Data Sources

The ALEX algorithm utilizes information from three data registries to estimate the average antimicrobial exposure of Danish slaughter pigs. The algorithm is based on the ideas of the LEA algorithm by Birkegård et al. (2017), however in a more robust and automated way. The LEA algorithm is a published algorithm developed to calculate the lifetime exposure to antimicrobials based on Danish register data in four manually executed steps, including hard coded adjustments on specific farms. Before we explain the ALEX algorithm, we describe the data registries behind the algorithm in the following.

CHR - the Central Husbandry Register

In the Central Husbandry Register (CHR) all Danish livestock are registered. All Danish farms are equipped with a unique CHR number linked to their geographical location. This CHR number serves as an identification key to associate specific farms with, for example, AMU and movements of pigs. Furthermore, the CHR register contains data on the type of animal species and number of animals on the farms. The CHR is updated on an ongoing basis, and the farmers are required to update the information in the register at least once a year (Fødevarestyrelsen, 2020a). All farms are also registered in Central Business Register under a CVR number, which is a unique number used for identifying all companies in Denmark. While the CHR number refers to a specific farm at a specific geographical location, the CVR number refers to the company and therefore the owner of the farm. From a CVR number it is possible to see the number of companies (farms) a farmer owns. Therefore, multiple farms can have the same CVR number (i.e. the same owner) but only one farm can be registered under a CHR number.

VETSTAT

VETSTAT is a national registry containing information about prescription drugs for veterinary use in Denmark. The drugs for production animals are prescribed at age group level within a herd for each farm. VETSTAT holds detailed data on the drugs purchased, including data on active compounds, strength, route of administration and amount prescribed (Stege et al., 2003). The purchased drugs are registered for the three different production stages: sows, weaners and finishers. The prescription data does not distinguish between purchases for piglets and sows, as all the records are registered for sows. The VETSTAT data utilized in our work have been cleaned in relation to the number of packages purchased, animal code and age group code. First, all registered purchases without animal species code were altered according to information on animals from the Central Husbandry Register (CHR). If animal species could not be resolved, the observation was rejected. Next, all registered purchases without age group code were altered according to information of age group from the CHR database. If the age group could not be resolved, the observation was rejected. Finally, since all registrations of drugs are included in VETSTAT, drugs that have been returned i.e. unused antimicrobials returned to the pharmacies, are also included in the data. Therefore, to clean the data, the observation of the purchased drug and its return were disregarded during the data preparation process. Prescription patterns vary over time and prescribed AMU in a farm are not necessarily used in the same month as they were prescribed. Parenteral AMs are often prescribed many months apart, in particular at farms with finishers only. Prescriptions in VETSTAT are registered the day the AM is sold, but not the day it is used.

Pig Movement Database

In Denmark, all movements of pigs between farms are registered in the Pig Movement Database. This means that it is possible to map production networks by tracing which farms are trading batches of pigs. Usually, pigs are moved from one farm to another when they enter a new rearing period. The pigs are not registered individually, so it is not possible to uniquely trace the path of a specific pig. However, the CHR and CVR number of both the sending and receiving farms and information about the number of pigs traded is available (Fødevarestyrelsen, 2020b).

The ALEX algorithm

The overall goal of the ALEX algorithm is to calculate the most plausible antimicrobial exposure for a given batch of Danish slaughter pigs during the full production period, i.e. from farrowing to slaughter. The algorithm is called ALEX since it estimates the Average Lifetime (antimicrobial) EXposure. The algorithm estimates the average exposure in each of the age stages, but it also provides a lifetime estimate. Based solely on the CHR number from the farm sending the pigs to slaughter and the slaughter date, the algorithm utilizes cleaned versions of the VETSTAT, CHR and Pig Movement databases to calculate an estimate of average antimicrobial exposure for the particular batch. The algorithm is implemented as a function in R based on the data.table package. The data.table package is based on data.frame but gives very fast and memory-efficient solutions such as join on intervals and rolling joins (Dowle and Srinivasan, 2019). As mentioned above, the function back-traces all potential combinations of locations of farms in the given production network and estimates the AMU for these paths based on the CHR number from the slaughter pig farm and slaughter date input. A weighted average of the AMU for the identified paths is derived from this depending on the proportion of pigs coming from each path of the production network. Thereby the algorithm can be divided into two main steps, *back-tracing* and *estimating and weighting*. In the following, the steps will be described in words. The pseudo code for the algorithm is provided in Listing 1 in the Supplementary Material.

Back-tracing

Based on a slaughter date and CHR number associated with a given batch from a finisher farm, the ALEX algorithm searches the Pig Movement Database for movements between farms with weaners to the finisher farm within a pre-specified time window. Then the ALEX algorithm does a second search in the database to identify movements from piglet farms to the weaner farms identified in the first search. In this way, the production network of the given finisher batch is determined. In Denmark, the movement pattern is reasonably stationary with most farms receiving animals from the same farms following a fixed schedule. In the Danish Pig Movement register, only number and species of moved animals are registered, but not the age group of the animals. Thus, it is not possible to trace a specific pig, and in some cases, it is not even possible to determine the age group between the movements. However, information in the CHR Register can, in some cases, be used to establish the age group. For example, if a movement between a farm registered with sows and weaners to a farm with only finishers is registered, then it is possible to classify the movement as a weaner-to-finisher (wf) movement since the receiving farm only holds finishers. In addition, some farms have internal production of piglets and/or weaners, although movements between age groups within a farm are not registered as a movement in the database. Thus, the internal production needs to be estimated. This is achieved by calculating

$$\text{internal}_{pw} = \text{sows [\#]}\cdot\text{weaners produced per sow per day [\#/day]}\cdot\text{size of movement window [days]}$$

$$\text{internal}_{wf} = \frac{\text{number of weaners [\#]}}{\text{average time as weaner [days]}} \cdot \text{size of movement window [days]}$$

The internal production of weaners is calculated as the average number of weaners produced by a sow in one year times the number of sows registered in the CHR database. This is then multiplied by the number of days in the moving time window considered in order to estimate how many pigs we expect to be internally moved within this specific period. Similarly, the internal production of finishers is estimated based on the number of weaners registered in the CHR database.

A maximum limit is implemented for the internal production to avoid overestimation. The limit is implemented because movements of pigs out of farms that have internal production are not considered. The limit is based on the number of weaners and finishers registered in the CHR for the specific farms.

Estimation and weighting

After determining the most plausible production network based on the back-tracing, the AMU for the identified farms is calculated and weighted in relation to the number of pigs moved between the farms. The estimated antimicrobial exposure is calculated as the average dose used for treatment of one kilogram pig

$$AMU_X\ [kg\ pig{\cdot}day] = \frac{\text{purchased antimicrobials}\ [mg] \cdot \text{time in rearing period}\ [days]}{\text{number of pigs}\ [\#] \cdot ADD_X\ [mg/kg] \cdot \text{purchase time window}\ [days]}$$

where X indicates the antimicrobial class of interest and ADD is the information about the average daily dose for the given antimicrobial class for pigs retrieved from VETSTAT. The purchases of antimicrobials are smoothed over the time period in question (i.e. the expected time period of the pig being in the piglet, weaner or finisher state, respectively) extended by 180 days before for each of the relevant farms. The AMU is computed for the twelve antimicrobial groups: *Aminoglycosides, Amphenicols, Lincosamides, Macrolides, Simple penicillins, Extended penicillins, Sulfonamides (incl. trimethoprim), Tetracyclines, Pleuromutilins, Cephalosporins, Fluoroquinolones* and *Other.* In addition, the AMU is also computed for 38 different active components, if more detailed knowledge is needed. The AMU is calculated for each of the three age groups, but also summarized as a lifetime exposure. The life time exposure for a drug class is calculated by adding the AMU calculated for each of the rearing periods. This is possible since the unit ($[kgpig \cdot day]$) of AMU_X is independent of the weight of the pig, which varies considerably within and between the age groups. As mentioned above, the prescription data in VETSTAT does not distinguish between piglets and sows. However, the unit used in ALEX is not based on the weight of the treated pigs and the antimicrobial exposure of sows has been shown to effect the AMR levels of their piglets Callens et al. (2015). The AMU for piglets is therefore calculated based on the prescriptions for sows. If of interest, it is also possible to get the estimated AMU divided into route of administration (i.e. peroral or parenteral).

An example and illustration of a back-tracing and the weighting of AMU can be found in Figure 1. In this scenario, the slaughter batch from FARM 1 is traced back to one weaner farm, FARM 2, and the weaner batch is traced back to FARM 3. In addition, FARM 2 has an internal production of weaners, while FARM 1 has an internal production of both piglets and weaners. The estimated movements are indicated by the arrows. The upper dashed lines indicate the two movement windows and the three lower dashed lines indicate the smoothing period for antimicrobial purchases for each of the three age groups. In this case, it is not possible to determine uniquely where a given slaughter pig from this batch has been located during its life cycle and therefore a weighting based on the probability is appropriate. The weaners come from FARM 1 or FARM 2 in this case. If 2/3 are estimated as internal production on FARM 1 and 1/3 is sent from FARM 2, then the corresponding AMU in this age group is weighted accordingly. The piglets might originate from internal production on FARM 1, internal production on FARM 2 or from FARM 3. The AMU for piglets from FARM 1 will be weighted with 2/3, since 2/3 of the weaners are estimated to come from FARM 1. If FARM 2 has an estimated internal production of 1/4 and receives the last 3/4 from FARM 3, then the AMU for piglets from FARM 2 will be weighted 1/3*1/4, while the AMU for piglets from FARM 3 will be weighted 1/3*3/4.

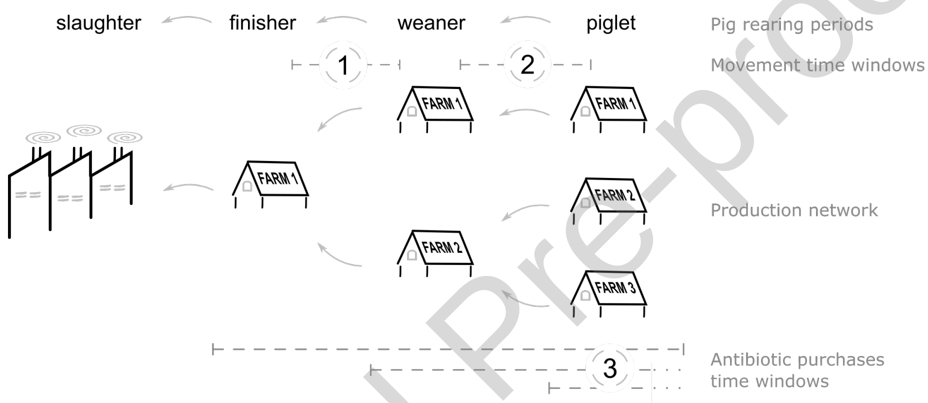


Figure 1: Diagram of the ALEX algorithm. The algorithm traces movements of (1) weaners to finishers and (2) the piglets to weaners in the Pig Movement Database based on a given CHR number and slaughter date. Also internal production is estimated based on information in the CHR register. The AMU is calculated based on VETSTAT registrations and weighted in relation to the trace and probability of locations (3). This illustrates how pigs are 'back-traced' and why it is not always possible to find the exact farm of origin for the slaughter pig.

Default parameters

The ALEX algorithm uses a number of default parameters on Danish pig production regarding the average number of days in the different production units and the size of movement time windows and antimicrobial purchase time windows. These parameters can be modified relatively easily if needed.

However, it is not recommended to change them if the algorithm is used for Danish pig production since these parameters are selected in a optimal way based on existing knowledge in order to get the most accurate and complete results. The movement time windows are based on weight gain statistics (Jessen, 2015; Birkegård et al., 2017) and the size of purchase windows is chosen to reflect the AMU on the farm in the period of interest, taking into account how prescriptions are registered in VETSTAT. The default parameters can be found in Table 1 in the Supplementary Material.

Successful trace

The output of the ALEX algorithm is quality controlled to avoid meaningless estimates. This is ensured by calculating and outputting a number of variables related to the management of the production and verification. Among other things, the additional output variables cover the number of farms identified in the production network, the number of owners in the network and different completion variables used to measure the completion of the trace. A table describing all output variables can be found in Table 2 in the Supplementary Material.

If the ALEX algorithm does not identify any movements from weaner to finisher or piglet to weaner farms, and if no internal movement can be estimated, the trace is regarded as a failed trace. Additionally, the traces are quality checked by the following:

(i) the proportions between estimated number of moved piglets and produced weaners, and estimated number of moved weaners and produced finishers are higher than 50%

(ii) the fraction of the movement chain that is complete is higher than 80%

(iii) the number of farms detected in a network is less than 8

Criteria (i) and (ii) are implemented to allow for discrepancies between the real world and the recordings in the registers, while criterion (iii) is implemented based on findings in (Anonymous, 2021).

A successful trace is therefore characterized by a complete traceable production network which fulfills criteria (i)-(iii). The proportion between estimated number of moved piglets and estimated production of weaners and estimated number of moved weaners and estimated number of finishers in criterion (i) is set to 50 % to accommodate possible discrepancies between information in the CHR and reality. This means that less than 50 % of the moved pigs from a farm can be accounted for based on the number of pen places registered in the CHR, i.e. less than 50 % of weaners or less than 50 % of finishers from the respective farms. The completeness of 80 % in criterion (ii) is the fraction of the full movement chain that is accounted for.

Shiny App

The R package 'Shiny' is a library of elements aiding an interactive representation and visualization of analyses performed in R. By wrapping the code, it is possible to build an interactive interface which allows other users to interact with the data and analyses without knowledge about the code behind (Chang et al., 2020). Based on the output of the ALEX algorithm, a Shiny is developed to visualize the farms in the network and the estimated AMU for each rearing period for a traced batch of slaughter pigs.

Mixed Effect models

To compare the output of the LEA and the ability of ALEX algorithms to describe the association between antimicrobial resistance genes (ARG) and AMU, mixed effect models are used. The analyses were performed in R using the 'lme4' and 'lmertest' packages. There was only one data set available for the comparison of the two algorithms. The data set consists of ARG samples collected from Danish slaughter pigs in 2015 and 2017, where the LEA algorithm was previously used to trace the sampled slaughter pigs and estimate AMU. Therefore ALEX was run for the same slaughter batches in order to compare the two. The structure of the mixed effect models was based on the findings in Anonymous (2021), having the exposure variables (estimated AMU of tetracycline for each rearing period) and a variable describing the number of farms in the production network (1, 2 or more than 2) as fixed effects in the model and the finisher farm (where the slaughter pig originates from) as random effect. Square root transformation was applied to the exposure variables based on residual analysis, and three different models were formulated with the levels of tet(W), tet(O) and tet(Q) as response variables. The models were reduced by backwards elimination and Bonferroni correction of the significance level to only contain the significant variables.

Tracing of all slaughter pigs in Denmark

The ALEX algorithm was used to investigate the changes in antimicrobial exposure of Danish slaughter pigs from 2015 to 2019. First, all movements of slaughter pigs to slaughter houses in 2015 were identified in the Pig Movement Database. The first batch from each of the farms sending at least one batch of minimum 20 pigs for slaughter in the first quarter of 2015 was then traced by the ALEX algorithm. The same was done for slaughter movements in 2019. The farms that were traceable with ALEX in both 2015 and 2019 were used for further analysis.

To evaluate the effectiveness of the ALEX algorithm, all farms sending pigs for slaughter during 2019 were traced. The first slaughter batch from each of the finisher farms sending at least one batch for slaughter in each quarter was traced. The effectiveness was then evaluated by measuring the total number of traceable farms.

Smoothing method and sensitivity analysis

The AMU was smoothed for each farm by calculating the average exposure per day of one pig in the specific rearing period for the specific farm during the considered period. The AMU can be smoothed and summarized by the different AM classes, active compound or route of administration. The period where the AMU is smoothed over is the relevant period where the pig could have been on the specific farm and 180 days prior to this. This smoothing period was chosen to account for the way data is registered in VETSTAT, namely that it is registered when the AM is purchased but not the day when it is used. A sensitivity analysis of the size of the purchase windows and the size of the movement windows was carried out by manually changing the parameters one by one and evaluating the impact on the results.

3. Results and discussion

The primary goal of the ALEX algorithm is to estimate AMU in Danish pig production in a fast, robust and automated way. These estimates can then be used to study the trends in AMU and their relation to data on

AMR, based on analyses of fecal samples, for example. In the following, we present two uses of these estimates: An interactive visualization tool and a comparison of AMU for individual farms in 2015 and 2019 reflecting a change in national treatment policy as a consequence of the changes in the yellow card scheme implemented in Denmark to control and limit the AMU in pig production (Antunes and Jensen, 2020).

Example of usage: Interactive visualization

Developing an algorithm to manage large amounts of data of great complexity and produce estimates such as AMU necessitates a graphic interface that can visualize the output results clearly. In addition to the fast and robust ALEX algorithm, a Shiny app was developed in R to visualize the output results. The Shiny works directly on the output of the ALEX algorithm and provides an interactive map with the identified farms and movements together with a graphical overview of estimated AMU. The Shiny serves as a tool for investigating and understanding the complex trading and movement patterns in production networks for specific slaughter pig batches. In Figure 2, the layout of the Shiny is shown.

Example of usage: Compare tetracycline and macrolide exposure in 2015 and 2019

All farms sending a batch of minimum 20 pigs to slaughter in the first quarter of 2015 and 2019 were identified in the Pig Movement Database. The first slaughter batch for each of these farms in this period was traced by the ALEX algorithm. The estimated AMU for the intersection of traceable farms in 2015 and 2019 was then compared. This means that, by using the ALEX

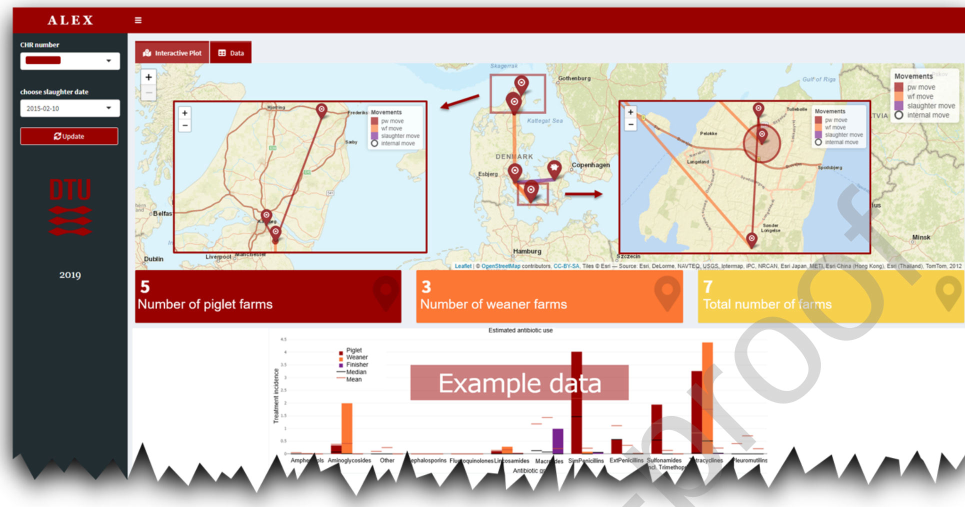


Figure 2: Layout of the shiny app developed in R to visualize the results of the ALEX algorithm interactively.

algorithm, a direct comparison of antimicrobial exposure during the complete lifetime and in each rearing period of an average slaughter pig from a specific farm can be performed. Slaughter batches from 1482 different farms (CHR numbers) were traceable in both 2015 and 2019 (out of 3120 identified farms). The results of the ALEX algorithm allow for both a comparison of the estimated lifetime exposure and also a comparison within each of the age groups. Figure 1 in the Supplementary Material shows the estimated total AMU for these farms in 2015 and 2019, respectively. In the following example, we focus on the results of tetracycline and macrolide exposure. In Figure 3 the distributions of the change in estimated lifetime AMU from 2015 to 2019 grouped by the amount of AMU in 2015 are shown for tetracycline (Figure 3a) and macrolides (Figure 3b). The farms that had a large tetracycline exposure in 2015 are also the farms that had the biggest reduction in tetracycline use in 2019, while the farms where the slaughter pigs already had a low exposure to tetracycline in 2015 had a median of 0 in 2019. For macrolides, the slaughter pigs that had a high exposure to macrolides in 2015 also seem to show a decrease in macrolide use in 2019. However, it is notable that the production networks with low or no macrolide exposure in 2015 tended to show increasing use of macrolides in 2019 (the median is greater than 0 for this group). The Supplementary Material includes figures of tetracycline and macrolide exposure in 2015 and 2019 for these slaughter batches, split into the age groups (see Figure 2 in the Supplementary Material). Note that the mean estimated exposure to tetracycline decreased from 2015 to 2019 for all three age groups, while it increased for macrolides for all three age groups. This is in good agreement with the findings reported by DANMAP, since the *differentiated yellow card initiative* was implemented in Danish pig production in 2016 to reduce the use of certain antimicrobials, in particular tetracycline (DANMAP, 2021). The main idea behind the yellow card initiative is that pig farms receive a yellow card from the authorities if they are using too much antimicrobials. The yellow card is followed by a period of 9 months to reduce consumption of antimicrobials and prepare a follow up action plan if needed. The updated yellow card scheme included different weights for the different antimicrobials when calculating how much is used on the farms. The weights are decided depending on how critical the drug class is for human treatment.

Figures showing the distributions of change in macrolide use for different groups of farms are in the Supplementary Material (Figure 3). The farms are grouped depending on the size of the change of tetracycline use and the figures are split between the three age groups. For the piglet group, there is no clear trend, although the tails of the distributions for the farms with the biggest reduction in tetracycline use are skewed towards increased macrolide use. From the figures it is also observed that a large proportion does not change the use much. This implies that the farms that had the biggest reduction in tetracycline use from 2015 to 2019 are also the farms that tend to increase their macrolide use.

Comparison

The ALEX algorithm was developed based on the LEA algorithm by Birkegård et al. (2017). As mentioned above, the algorithm was published in 2016 as a tool to estimate the antimicrobial lifetime exposure in Danish slaughter pigs. We present a comparison of the ALEX and LEA algorithms below.

- The ALEX algorithm is wrapped into one function, whereas the LEA algorithm is split into different scripts and not wrapped into a function.
- The ALEX algorithm is automated, which means that when a CHR number, a slaughter date and access to standardized registry data are provided, then the algorithm runs with just a function call. The register data need to be gathered and the variable names standardized. The LEA algorithm does have some manual steps, where corrections are applied on specific farm data.
- The number of pigs estimated in the LEA algorithm can be calculated to be less than zero, whereafter an adjustment based on the CHR

database is calculated.

- The runtime of the ALEX algorithm is much shorter per trace compared to the LEA algorithm.

Besides the above, the two algorithms were also compared by investigating which of the estimated AMUs produced by the algorithms are better associated with AMR data. The LEA algorithm was used to estimate AMU for some farms where AMR data were collected in 2015 and 2017. More details on the data collection is described in Anonymous (2021). The ALEX algorithm was used on the same subset of data as the LEA algorithm to compare the two algorithms. Different model structures were applied on the basis of previous work in Anonymous (2021). Thus, the most widespread AMR genes in these samples, tet(W), tet(O) and tet(Q) were used as the response variable in three separate models. The data consist of 681 samples from 524 farms, 663 of the samples are from unique farms but with different sample dates. In Figure 4 the traces by the ALEX algorithm are divided into unique traces, i.e. if the production chain was identifiable, or into traces that show more than one plausible route. A trace is unique if only one piglet farm and only one weaner farm (including internal production) are identified in the network. The figure shows that 432 out of the 663 traces are uniquely determined by the ALEX algorithm, thereby offering a precise estimate of AMU for these pigs. The AMU of tetracycline for piglets, weaners and finishers and the number of farms ('Type') were included in the models before backwards elimination. Comparing the Akaike Information Criterion (AIC) of the two models for tet(W) by using the AMU estimates of the LEA algorithm and the ALEX algorithm as input showed that using the estimate of the ALEX algorithm gave the lowest AIC and therefore the ALEX algorithm is better at describing the relationship between AMU and tet(W) resistance. For tet(Q), the AIC was slightly lower for the LEA algorithm, while it was lowest for the ALEX algorithm in the tet(O) model (see Table 1). The results of the ALEX algorithm are comparable to LEA results for this data set, and the ALEX algorithm offers several performance advantages.

	Variables	**AIC**
	Gene: tet(W)	
LEA	Type, tet_{weaner}, $\text{tet}_{finisher}$	941.9
ALEX	Type, tet_{weaner}, $\text{tet}_{finisher}$	894.0
	Gene: tet(Q)	
LEA	Type, $\text{tet}_{finisher}$	1538.2
ALEX	Type, tet_{weaner}, $\text{tet}_{finisher}$	1542.7
	Gene: tet(O)	
LEA	Type, tet_{piglet}, $\text{tet}_{finisher}$	933.6
ALEX	Type, tet_{piglet}, $\text{tet}_{finisher}$	925.3

Table 1: Table of variables in reduced mixed effect models and AIC values for comparing output of the LEA and ALEX algorithms.

Evaluating effectiveness by successful traces

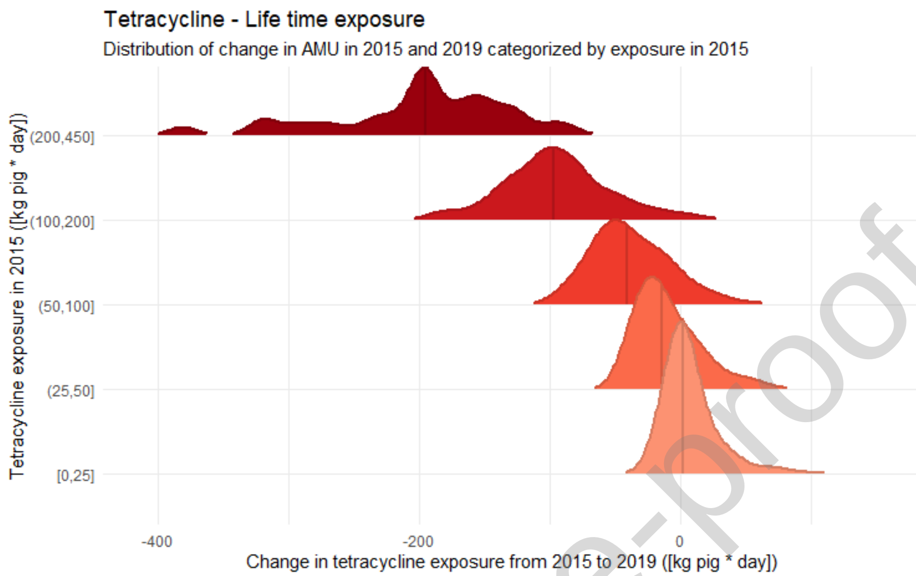
The ALEX algorithm was used to estimate AMU for all slaughter pigs in Denmark during the four quarters of 2019. The effectiveness of the ALEX algorithm was evaluated by investigating the percentage of successful traces i.e. how many of all slaughter pig farms sending pigs for slaughter are traceable and fulfill criteria (i)-(iii) using ALEX within each quarter. The effectiveness was between 75 - 85 % for the four periods (results not shown here). The most common reason for a failed trace was because movements were not registered in the Pig Movement Database, but incorrect information in the CHR also contributed to failed traces. Incorrect information in the CHR registry covers errors in relation to animal species and number of animals within each age group on the farm. These often occur when farmers forget to update the information when changing their production. The performance and accuracy of the algorithm of course depends heavily on the information in the provided data and the quality of these data. Missing and inadequate information in all of the registries or mismatch between the information in the different registries gives rise to estimation issues (Birkegård et al., 2018). The mortality of piglets is indirectly accounted for by the parameter describing the number of live weaners produced per sow, while the mortality of weaners and finishers are not, but this is compensated for by allowing the completeness measure to be less than 100% The main challenges of working with VETSTAT are explained in detail in (Dupont et al., 2017) and cover issues such as incorrect information, difference between reported date of purchase and actual date of usage and negative entries.

Smoothing methods

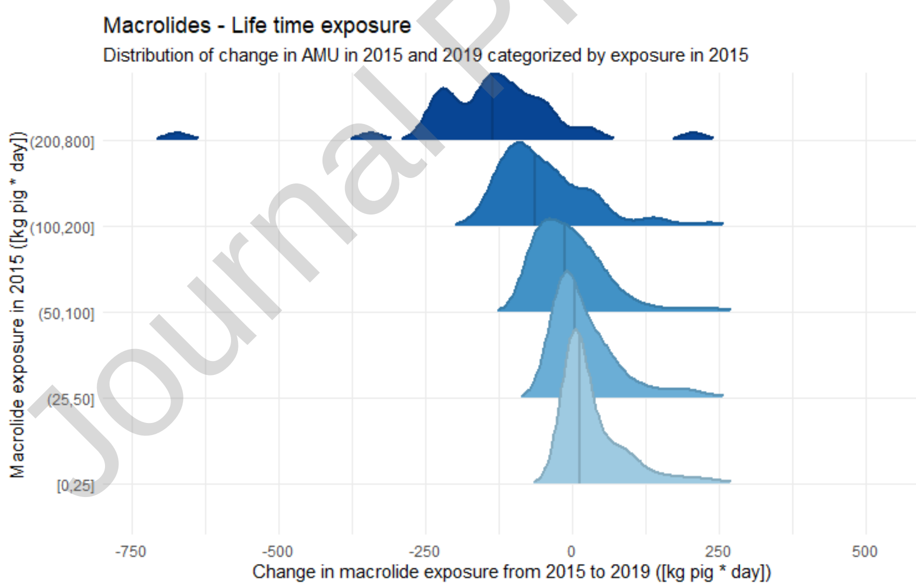
In the ALEX algorithm, different smoothing methods can be applied depending on the desired estimate. Thus, the smoothing method can vary from smoothing over antimicrobial class to active compound or route of administration, as also described in (Andersen et al., 2018). A sensitivity analysis of the size of the time windows for movements and antimicrobial purchases was performed. Increasing the window sizes of the movement windows increased the number of successful traces a little, although a higher incidence of insufficient traces was observed. Decreasing the window size decreased the number of successful traces. The estimates of mixed effect models for different sizes of the purchase window were very similar for all models except when the window size was increased by 50 %, where an additional antibiotic class was included in the model. The results can be found in Section 5 the Supplementary Material.

4. Conclusion

The ALEX algorithm provides a fast and robust approximation of AMU in Danish slaughter pig production based only on secondary data from registries. The results of the ALEX algorithm can be used as a fast, robust and transparent way of mapping production networks and estimating AMU within these. The results can also be used to investigate the influence of AMU on AMR at national scale. In addition, there is a potential of the algorithm to contribute to future research studies. The tracing of the production chain can be very useful in investigating subjects such as disease transmission, disease treatment and identification of risk factors. The algorithm might also be valuable for other countries with similar pig production and data availability.



(a)



(b)

Figure 3: Distribution plots of change in estimated tetracycline and macrolide lifetime exposure from 2015 to 2019 for the slaughter pigs batches traced by ALEX in both years. The distributions are divided based on the amount of estimated AMU in 2015. The farms are grouped based on AMU in 2015, which is shown on the y-axis as ranges. The color gradient is added for readability. The darkest colors represent the farms that had the highest use in 2015.

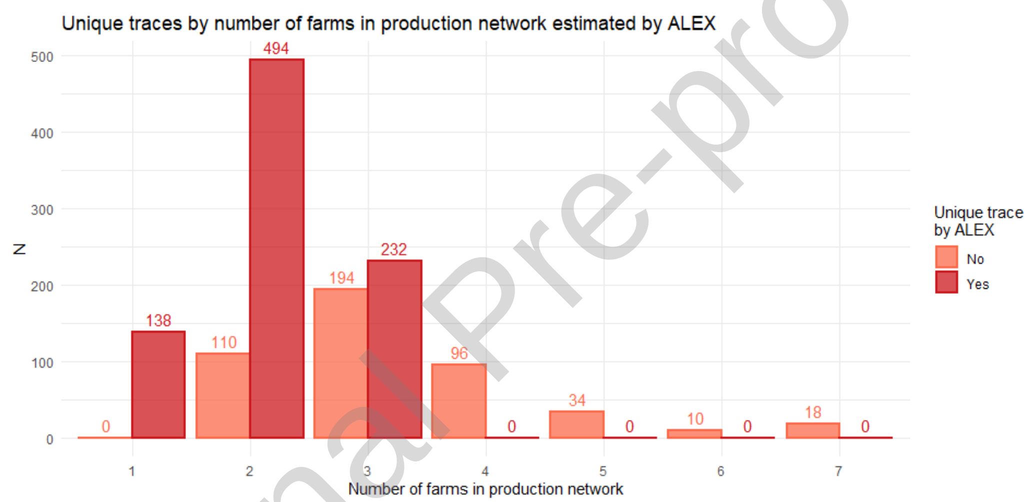


Figure 4: Number of uniquely traced pig productions by the ALEX algorithm. The data originate from the comparison of the ALEX and LEA algorithms and in total 663 Danish slaughter pig batches were traced (in 2015 and 2017, respectively) and 432 of these were uniquely determined.

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