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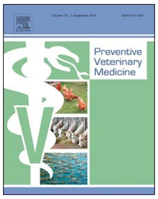

# Computional algorithm for lifetime exposure to antimicrobials in pigs using register data—The LEA algorithm

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## ABSTRACT

Accurate and detailed data on antimicrobial exposure in pig production are essential when studying the association between antimicrobial exposure and antimicrobial resistance. Due to difficulties in obtaining primary data on antimicrobial exposure in a large number of farms, there is a need for a robust and valid method to estimate the exposure using register data.

An approach that estimates the antimicrobial exposure in every rearing period during the lifetime of a pig using register data was developed into a computational algorithm. In this approach data from national registers on antimicrobial purchases, movements of pigs and farm demographics registered at farm level are used. The algorithm traces batches of pigs retrospectively from slaughter to the farm(s) that housed the pigs during their finisher, weaner, and piglet period. Subsequently, the algorithm estimates the antimicrobial exposure as the number of Animal Defined Daily Doses for treatment of one kg pig in each of the rearing periods. Thus, the antimicrobial purchase data at farm level are translated into antimicrobial exposure estimates at batch level. A batch of pigs is defined here as pigs sent to slaughter at the same day from the same farm.

In this study we present, validate, and optimise a computational algorithm that calculate the lifetime exposure of antimicrobials for slaughter pigs. The algorithm was evaluated by comparing the computed estimates to data on antimicrobial usage from farm records in 15 farm units. We found a good positive correlation between the two estimates.

The algorithm was run for Danish slaughter pigs sent to slaughter in January to March 2015 from farms with more than 200 finishers to estimate the proportion of farms that it was applicable for. In the final process, the algorithm was successfully run for batches of pigs originating from 3026 farms with finisher units (77% of the initial population). This number can be increased if more accurate register data can be obtained.

The algorithm provides a systematic and repeatable approach to estimating the antimicrobial exposure throughout the rearing period, independent of rearing site for finisher batches, as a lifetime exposure measurement.

## 1. Introduction

In recent decades, authorities have enforced regulatory initiatives to regulate the usage of antimicrobials in an attempt to reduce antimicrobial resistance (AMR) in livestock animals. However, there is a general need for a quantitative assessment of the relationship between AMR and antimicrobial exposure in livestock animals. In studies of this relationship, reliable estimates of antimicrobial exposure in batches of livestock animals during different rearing periods are needed. Here, we define a batch of animals as animals sent to slaughter on the same day from the same farm. In modern conventional pig production, the time from birth to slaughter is approximately six months. Therefore, we assume that the antimicrobial exposure during the entire lifetime of pigs influences the levels of AMR found at slaughter. Previous studies performed in pig farms have shown that AMR at one time point was associated with antimicrobial exposure in previous rearing periods (Dunlop et al., 1998; Rosengren et al., 2007; Varga et al., 2009). Furthermore, in population studies estimates of antimicrobial exposure

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*Abbreviations:* LEA, lifetime exposure to antimicrobial; CHR, Central Husbandry Register; PMD, Database of Pig Movements; ADD, $_{kg}$Animal Defined Daily Dose for treatment of one kg pig

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must reflect the actual use in batches during the lifetime of the pigs. This can be difficult to obtain when using farm level register data because pigs are often moved from the farm, where they were born.

In this study, we present a computational algorithm that use data from registers to translate antimicrobial purchase data on farm level to antimicrobial exposure on batch level. The antimicrobial exposure is calculated for three rearing periods (piglet, weaner, and finisher period) and as a total estimate of the amount of antimicrobial exposure. We call this the LEA approach. The concept of the LEA approach was presented by Andersen et al. (2017), who showed that the LEA estimate explained more of the variation in the AMR levels in finishers than estimates of the antimicrobial usage in finisher units only or at the farms in general did. The principle of the LEA approach presented by Andersen et al. (2017) was a database estimation of the amount of antimicrobials that finishers at ten farms had been exposed to during their lifetime and independent of rearing site. Here, we further develop the approach to provide the LEA estimates for larger population using a systematic computational approach.

In Denmark, all purchases of antimicrobials for use in livestock are registered in the national veterinary medicine register (VetStat) (Stege et al., 2003). Antimicrobials are prescription-only drugs and only sold through veterinarians, pharmacies, or feed mills. The prescribing veterinarian has to reach a diagnosis prior to prescription. Thus, antimicrobials used for prophylactic treatments and as growth promoters are prohibited in Denmark (Anonymous, 2016a). All movements of pigs in Denmark are mandatory to register in the national database for pig movements (PMD). Coupling information on movements of pigs and antimicrobial purchases allows tracing pigs to the farms where they have been and calculate the amount of antimicrobials they were exposed to in the different rearing periods. This is the essence of the LEA approach, which generates data on antimicrobial exposure to batches of pigs with a high resolution both in time (exposure in different rearing periods) and space (usage at different farms). High temporal and spatial resolution is critical in the study of how antimicrobial exposure influences the levels of AMR in livestock animals (Collineau et al., 2017). Henceforth, the LEA estimates may be used for studying the association between antimicrobial exposure and AMR at batch level in population studies and risk assessments where collection of primary data about the antimicrobial usage at farm level is not feasible.

The objective of the presented work was to develop and optimise an algorithm designed to implement the LEA approach presented by Andersen et al. (2017) to the majority of slaughter pigs in Denmark. Furthermore, we validate the algorithm using farm data on actual antimicrobial usage. The algorithm was run on Danish farms with a conventional production of slaughter pigs to estimate the proportion of farms for which the algorithm is applicable.

## 2. Materials and methods

The LEA algorithm estimates the total amount of antimicrobial exposure during the lifetime of a batch of pigs. A batch was defined as a group of pigs sent from the same farm to the same slaughterhouse on the same day. Briefly, the algorithm was run for batches of finisher pigs starting at their date of slaughter. Based on the date of slaughter and identity of the farm with the finisher unit, the algorithm retrospectively estimates at which farm(s) they were reared as piglets and weaners. This tracing process is Step 1 (Estimating the age group of moved pigs) and Step 2 (Production chain trace back) of the algorithm. Subsequently, the antimicrobial exposure per pig per day was estimated for the batches for each of the rearing periods, as described in Step 3 (herd size calculation) and Step 4 (antimicrobial exposure smoothing) of the algorithm (Fig. 1). Finally, the lifetime exposure to antimicrobials was calculated as the sum of antimicrobial exposure in the three rearing periods.

### 2.1. Register data used by the LEA algorithm

The LEA algorithm used data from three national registers: VetStat, the PMD, and the CHR. The databases are owned by the Danish Veterinary and Food Administration. More information regarding these three databases can be found in Supplement material 1.

Data from the CHR were extracted twice – in September 2014 and in March 2015 – to account for changes in the farm demographics between the beginning and end of the study period. The number of pigs in each age group (weaners, finishers, and sows) was calculated as the mean of the two data extractions. The PMD data were extracted in April 2015, and data from VetStat were extracted twice – observations from 1st of September 2013 to 30th of April 2015 were extracted in June 2015 and observations for May 1st to July 1st were extracted in October 2015. The two subsets were subsequently merged.

In this paper, we define a farm as a premise housing pigs according to the CHR.

The algorithm only uses data from pharmacies, accounting for more than 99.9% of antimicrobials sold for use in pigs in the farms included in the present study (based on calculations from VetStat data).

### 2.2. LEA algorithm

The LEA algorithm operationally runs in four steps (Fig. 1): 1) Estimating the age group of moved pigs; 2) Production chain trace back; 3) Herd size calculation; 4) Antimicrobial exposure smoothing.

The algorithm deals with three rearing periods of a pig produced for slaughter at approximately 100 kg: the piglet period (birth-7 kg), the weaner period (7–30 kg weight) and the finisher period (30–100 kg, approximately).

In this study the LEA algorithm was applied to all Danish pig farms with more than 200 finishers (according to the CHR register data) who sent pigs to slaughter between January 1st and March 2015, 31st. For each farm, the batch of pigs that were sent to slaughter closest to the 15th of February 2015 was chosen.

The LEA algorithm was written and run in R version 3.2.2 (R Core Team, 2017). A brief description of each of the four steps follows, and further details are provided in Supplement 2.

#### 2.2.1. Step 1: estimating the age group of moved pigs

The PMD contains no information about the age of the pigs moved. In order to calculate the antimicrobial exposure defined by age group, this information must be estimated in order to track the pigs correctly and calculate the number of pigs. The age group was estimated based on:

i) The assumption that a slaughter pig is moved up to three times during its lifetime. The pig is first moved from piglet unit to weaner unit at a bodyweight of approximately 7 kg and then from the weaner unit to a finisher unit at a bodyweight of approximately 30 kg. The movement from a unit to the subsequent unit can happen within the same farm or between farms. The third and final move is from the finisher unit to the slaughterhouse at a bodyweight of approximately 100 kg. The only certain movement is to the slaughterhouse.

ii) The number of pigs moved. There is a limit to the number of pigs of a specific age group a vehicle may transport at once. We assumed that, in the majority of cases, the number of pigs transported would be as close to this limit as possible and consequently that the number of pigs moved would reflect the age group of the moved animals. We do not have an exact estimate for number of pigs moved that would reflect a specific age group. Therefore, we tested different settings (see the section "test of the parameter settings"). To distinguish between movements of sows and movement of finishers, the cut-off$_{\text{sow}}$ was defined as either 40 or 60 pigs per movement. To distinguish between movements of finishers and