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RESEARCH

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Delivery strategies to improve piglets exposure to oral antimicrobials

Noslen Hernández¹, Béatrice B. Roques^{1,2}, Marlène Z. Lacroix^{1,2} and Didier Concordet^{1,2*}

Abstract

Background The widespread practice of delivering antimicrobials through drinking water to livestock leads to considerable variability in exposure levels among animals, raising concerns regarding disease outbreaks and the emergence of antimicrobial resistance. This variability is primarily driven by three pivotal factors: fluctuations in drug concentration within water pipes, variances in drinking behavior among animals, and differences in individual pharmacokinetic parameters. The objective of this study is to develop and evaluate a strategy that tailors medication delivery based on the drinking patterns of pigs, aiming to improve medication distribution without increasing the overall dose of medication.

Results Our results demonstrate that several distribution strategies based on the animals' drinking behavior can effectively increase their overall exposure. These strategies include increasing the exposure of the least exposed animals, raising the average exposure, maximizing the exposure of the majority of the well-exposed animals, or increasing exposure to ensure that a Pharmacokinetics/Pharmacodynamics (PK/PD) criterion reaches a threshold value for a large number of the animals. In summary, constructing an effective distribution strategy for drinking water requires optimizing a specific criterion. The various criteria and methods for optimizing them are detailed.

Conclusions As examples, this article demonstrates that incorporating the drinking behavior into the delivery of amoxicillin results in an increase in the percentage of piglets reaching an AUC/MIC ratio greater than 25h. Specifically, with *Pasteurella multocida*, the percentage rises from 30% to at least 60%, while with *Actinobacillus pleuropneumoniae*, it increases from 20% to more than 70%.

Keywords Exposure to antimicrobials, Pharmacokinetics/pharmacodynamics, Drinking behavior

Background

The use of antimicrobials in group-raised animals has emerged as a significant concern, particularly in pig farming. Antimicrobials are typically administered to pigs in various ways, with one prevalent approach involving their addition to drinking water. This method offers

a consistent and convenient way to treat large groups of pigs. However, it can lead to considerable variability in exposure levels, as animals do not consistently receive the same dosage of medication over time. Consequently, some animals may be underexposed, while others may be overexposed [1].

The balance between under- and over-exposure of pigs to antimicrobials when those are treated by medicated water, is a critical issue in modern livestock farming. While overexposure contributes to the alarming rise of antibiotic-resistant commensal bacteria, underexposure is equally important. Underexposure not only increases the risk of disease outbreaks among animals, leading to suffering and economic losses for farmers, but also plays

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a pivotal role in fostering the development of antibiotic-resistant bacteria, posing a significant public health risk [2]. Addressing this challenge requires the development of optimal delivery strategies that promote responsible antimicrobial use on pig farms.

To make progress in this area, it is essential to better understand the causes of variability in exposure levels. A recent study on pig exposure to antimicrobials administered through drinking water [3] identified three main factors contributing to this variability:

- Variation due to the actual concentration of the drug in the drinking water. For instance, Vandael et al. [4] demonstrated significant fluctuations in drug concentration at the end of the pipeline, often failing to reach the recommended therapeutic range.
- Variation due to the diverse drinking behaviors of the animals, i.e., differences in the amount of medication consumed by each individual pig.
- Variation due to different pharmacokinetic parameters among pigs, resulting in differences in drug absorption and/or elimination (clearance).

A previous study [5] demonstrated that the effective concentration of the drug in the pipes supplying water to the drinkers, along with the animals' drinking behavior, are the most significant sources of variability in animal exposure to antimicrobials. In contrast, inter-individual variability in clearance and absorption rates was found to be a minor factor contributing to exposure variability.

The same study demonstrated that when amoxicillin or doxycycline is distributed in drinking water for three consecutive days, sufficient exposure to target common bacteria (e.g., *Pasteurella multocida* and *Actinobacillus pleuropneumoniae*) is achieved in only a small percentage of animals. As a result, the currently recommended minimal course of duration for dosing amoxicillin or doxycycline in the water does not adequately cover a significant portion of the individuals.

Several solutions can be considered to address under-exposure in the group. The simplest approach is to increase the concentration of antimicrobials in the water. However, this method raises overall antimicrobial consumption, which can contribute to the emergence of resistance. Administering a loading dose at the start of treatment might help achieve effective therapeutic concentrations more rapidly in a larger number of animals and could partially reduce inter-individual variability [6]. However, loading doses are only feasible for antimicrobials with long terminal half-lives and good bioavailability. Another option is to modify the formulation to extend its half-life, but this is challenging for medications distributed through drinking water. An alternative approach,

which has not been extensively covered in the literature, is to adapt the distribution of medication based on the specific drinking behavior of the group of pigs being treated.

The key idea presented in this article is that increasing the concentration of medication in drinking water when piglets drink leads to a higher intake of medication and, consequently, elevated exposure. By tailoring antimicrobial distribution to the animals' drinking behavior, it becomes possible to achieve enhanced exposure for a substantial percentage of the animals while keeping the daily dose unchanged.

This article introduces strategies for customizing medication delivery based on drinking patterns, including increasing exposure for the least exposed animals, raising average exposure, maximizing exposure for the majority (95%) of well-exposed animals, or ensuring that a Pharmacokinetics/Pharmacodynamics (PK/PD) criterion is met for a large number (95%) of animals. These strategies are aimed at optimizing specific criteria for an effective distribution.

Material and methods

The animals were obtained from IFIP (Institut du Porc, Romillé, France), and all entered the study in good health. Each pen, ranging from 8 to 10 m² and housing approximately 17 piglets, was equipped with two connected feed dispensers and one water dispenser. Water dispensers were bowl drinkers that recorded the weight of the water before and after each drinking event when the animal approached its head to drink. Water was provided ad libitum. The weight, drinking times, and corresponding water consumption were recorded for 918 piglets housed in 54 pens, monitored from 28 to 60 days of age. Each piglet was fitted with a Radio-Frequency Identification (RFID) sensor attached to its ear, enabling individual identification during each recording. All piglets were maintained under uniform husbandry conditions, including consistent temperature and ventilation. Lighting was set from 9:00 to 17:00 each day. At the end of the experiment, individual water consumption profiles and weight variations were available for a 30-day of recording.

Model for water consumption

The data corresponding to each pig's water consumption can be viewed as a time series [7]. Occasional extreme values within these series reflect water intake levels that are inconsistent with physiological needs. These extreme values include not only water ingested by the pig but also water wasted, often due to pigs playing with the water. This section presents a model for detecting and adjusting for excessive water consumption.

As a first step, an additive model, represented by the following equation, was employed:

$$Q_{ik} = T_i(t_{ik}) + P_i(t_{ik}) + \varepsilon_{ik}. \quad (1)$$

Here, Q_{ik} denotes the observed volume of water consumed by the i -th piglet at time t_{ik} . This model decomposes the time series Q_{ik} into three fundamental components [8]. The trend term T_i captures the individual increase in water volume consumed over time, offering insight into the long-term underlying pattern in the data. The periodic term P_i captures the repeatability of the drinking pattern from one day to the next, spotlighting the periodic fluctuations in the data that occurs with a fixed frequency. The residual component ε_{ik} encapsulates variations not explained by the trend and periodicity terms, encompassing the unpredictable aspects of the time series.

The technical details regarding the parameter estimation of this model can be found in the Supplementary Material, section 1.

In the second step, the value of Q_{ik} was identified as an outlier if its corresponding residual, $\widehat{\varepsilon}_{ik}$, exceeded a certain threshold. Conversely, if the water consumption was not identified as an extreme value, it remained unchanged and was retained for use in the subsequent pharmacokinetic (PK) stage (technical details also appears in the Supplementary Material, section 1).

Model for pharmacokinetics

The daily quantities of antimicrobials to be diluted in the water, targeting dosages of 20 mg/kg for amoxicillin and 10 mg/kg for doxycycline, were calculated based on the number of animals, their average weight, and the average daily water consumption. Population pharmacokinetic models of amoxicillin and doxycycline in pigs have been previously studied [9, 10]. These models were employed to calculate the optimal strategies discussed in this article.

Ten sets of raw data were obtained from three pharmaceutical companies and an academic laboratory following oral (PO) or intramuscular (IM) administration of amoxicillin in pigs. As detailed in Rey et al. [9], all plasma concentrations were normalized to a standard dose of 20 mg/kg to develop the population pharmacokinetic model used in this study.

For doxycycline, as described in Del Castillo et al. [10], the population pharmacokinetic model was constructed using raw data obtained from a pharmaceutical company and an academic laboratory following oral and intravenous (IV) administration. Sterile 10 mg/mL solutions of doxycycline hydrochloride (Sigma-Aldrich, St-Quentin Fallavier, France) were prepared for IV dosing, while feed-grade premixes of doxycycline (Doxyval 40 Porc P/M) were provided by Laboratoires Sogéval, Laval, France.

A two-compartment model provides the more accurate description of the kinetics of these two drugs. The plasma concentration Z_t in a pig drinking a single dose D of medication at time $t = 0$ can be summarized as follows:

$$Z_t = D(f(t, \psi) + \sigma f(t, \psi)\varepsilon_t), \quad (2)$$

where ψ is the vector of individual PK parameters for the piglet, f denotes the expected plasma concentration, σ is the coefficient of variation of Z_t , and ε_t is a standard normal random variable independent of ψ .

By utilizing individual water consumption profiles along with previously published kinetic models, the expected concentration profile during the specified treatment period can be calculated. Specifically, if t_{ik} represents the k -th drinking moment of pig i , and D_{ik} denotes the dose of medication drunk at that moment, the expected drug concentration at time t is given by:

$$C_i(t) = \sum_k (D_{ik}(f((t - t_{ik})_+, \psi_i) + \sigma f((t - t_{ik})_+, \psi_i)\varepsilon_t)), \quad (3)$$

where ψ_i is the vector containing the PK parameters of the i -th piglet, and $(a)_+ = a$ if $a > 0$ and $(a)_+ = 0$ otherwise. For each piglet, 300 PK profiles were simulated.

The k -th dose of drug ingested by the i -th pig, D_{ik} , depends on the volume of water Q_{ik} consumed at that moment. Specifically, $D_{ik} = Q_{ik} \times F(t_{ik})$, where $F(t_{ik})$ represents the concentration of drug diluted in the drinking water at the time t_{ik} . In current practice, a constant concentration of the antimicrobial is maintained in the water throughout the day, such that the average dose is 20 mg/kg for amoxicillin and 10 mg/kg for doxycycline. Thus, the function F remains constant within each day but varies daily based on the average weight of the piglets.

To increase the animals' exposure during the treatment period, the concentration of the drug will vary throughout the day and over the duration of the treatment while keeping the overall dose unchanged. Let $F_0(t)$ denote the concentration of the drug, which is constant over a day and ensures doses of 20 mg/kg for amoxicillin and 10 mg/kg for doxycycline. Define $F(t)$ as $F(t) = F_0(t) \times G(t)$, where $G(t)$ represents the percentage of $F_0(t)$ allocated at time t , with the condition that $\int_0^{24} G(t)dt = 1$.

When the function $G(t)$ is constant, it indicates that the medication concentration in the drinking water remains constant throughout the day. Conversely, if $G(t)$ varies over time, it allows for adjustments in the medication concentration within the same day. Given the practical challenges of continuously adjusting the concentration, changes will be restricted to specific, predetermined times. In particular, two forms for G were investigated,

$$G_a(t) = \sum_{i=0}^{23} a_i 1_{\{i \leq t' < i+1\}}, \tag{4}$$

where $\sum_{i=0}^{23} a_i = 1$ and $t' = t - 24\lfloor t/24 \rfloor$ represents the hour within the day; and,

$$G_b(t) = \sum_{i=0}^{5 \times 24 - 1} b_i 1_{\{i \leq t < i+1\}}, \tag{5}$$

with $\sum_{i=0}^{5 \times 24 - 1} b_i = 1$.

The first function, G_a , allows for changes in concentrations during the day, but these changes remain consistent for each day of treatment. In contrast, the second function, G_b , enables varying concentration during the day, with different patterns applied for each treatment day.

The way of distributing the medication in drinking water can be summarized by selecting a particular function G , referred to as the antimicrobial distribution strategy. This strategy is defined by choosing specific values for a_0, a_1, \dots, a_{23} or $b_0, b_1, \dots, b_{5 \times 24 - 1}$. The function G_a (and similarly G_b) represents the fraction of the daily dose (or the fraction of the total dose over 5 days) to be administered during each time interval. For instance, under the usual strategy, the coefficients are $a_0 = a_1 = \dots = a_{23} = 1/24$ and $b_0 = b_1 = \dots = b_{5 \times 24 - 1} = 1/(5 \times 24)$. Hereafter, G_a and G_b will be referred to as the daily-fractionated strategy and the multi-day cumulative strategy, respectively.

Criteria to find optimal strategies

To determine an optimal strategy, it is essential to define the criterion that each type of strategy aims to optimize. In this article, all criteria are based on the area under the curve (AUC) of the average concentrations obtained over the entire treatment duration. Let $AUC_i^j(a_0, \dots, a_{23})$ (respectively $AUC_i^j(b_0, \dots, b_{5 \times 24 - 1})$) represent the average AUC over 5 days of treatment starting on day j , taking into account the drinking behaviour of the i -th individual for a strategy $(a_0, a_1, \dots, a_{23})$ (respectively $(b_0, b_1, \dots, b_{5 \times 24 - 1})$). Formally, these AUCs are defined as follows:

$$5 \times AUC_i^j(a_0, \dots, a_{23}) = \int_{24j}^{24(j+5)} \sum_k Q_{ik} F_0(t_{ik}) G_a(t_{ik}) (f((t - t_{ik})_+, \psi_i) + \sigma f((t - t_{ik})_+, \psi_i) \varepsilon_t) dt \tag{6}$$

and

$$5 \times AUC_i^j(b_0, \dots, b_{5 \times 24 - 1}) = \int_{24j}^{24(j+5)} \sum_k Q_{ik} F_0(t_{ik}) G_b(t_{ik}) (f((t - t_{ik})_+, \psi_i) + \sigma f((t - t_{ik})_+, \psi_i) \varepsilon_t) dt. \tag{7}$$

Four optimality criteria have been selected.

Criterion 1: Minimum AUC

This criterion identifies the strategy that maximizes the minimum average AUC across all individuals over the treatment duration. Thus, the optimal strategy is determined by the piglet with the lowest exposure during the treatment period.

Criterion 2: 5th percentile of AUCs

The second criterion is based on the 5th percentile of the average AUCs over the treatment duration. Choosing the strategy that maximizes this criterion involves disregarding the 5% of the lowest exposures and focusing on maximizing the exposures in the 95th percentile. This criterion assumes that lower exposures are likely to occur and are challenging to control.

Criterion 3: Inverse of the coefficient of variation of AUCs

Recall that the coefficient of variation (CV) of a random variable X is defined as $CV(X) = SD(X)/E(X)$, where $SD(X)$ represents the standard deviation of X and $E(X)$ represents its expected value.

Consequently, maximizing the inverse of the coefficient of variation of the average AUCs over 5 days, or equivalently minimizing the coefficient of variation, aims to identify the strategy that not only increases the average AUC across all piglets but also minimizes the dispersion of these AUCs.

Criterion 4: The area under the curve of the probability of target attainment (PTA) for a bacterium

The sensitivity of a bacterium to an antimicrobial is characterized by the minimum inhibitory concentration (MIC). Since not all bacteria have the same MIC, the sensitivity of the strain is described by a distribution of MICs. In this study, two bacterial families were considered: *Pasteurella multocida* and *Actinobacillus pleuropneumoniae*, whose MIC distributions for amoxicillin and doxycycline can be found on the EUCAST

database, created by G. Kahlmeter and J. Turnidge [11]. This database is regularly updated with additional data, all of which is curated by G. Kahlmeter and J. Turnidge [12]. The distributions are presented as “aggregated weighted distributions,” where each individual distribution is converted to contribute equally to the common aggregated distribution.

A global measure to quantify the exposure of a group of animals to an antimicrobial for a given bacterium is to calculate the percentage of “meeting” between an individual and a bacterium for which the AUC/MIC is large enough. For the antimicrobials of interest in this article, it is generally accepted [13] that the optimal dosing regimen should aim to ensure that as many individuals/bacteria as possible should have an AUC/MIC greater than 25h or 48h.

These thresholds are considered to ensure a bacteriostatic and bactericidal effect, respectively [14, 15]. Consequently, the commonly employed criteria are $P(AUC/MIC \geq 25)$ and $P(AUC/MIC \geq 48)$. While these thresholds can guide the selection of a dosing regimen, they are empirically derived; thus, alternative values may also be considered. A general index is proposed here to assess whether the chosen regimen provides adequate coverage for a sufficient percentage of individuals, given by:

$$AUC_{PTA}(a_0, \dots, a_{23}) = \int_0^{100} P\left(\frac{AUC(a_0, \dots, a_{23})}{MIC} \geq x\right) dx, \tag{8}$$

which increases as a larger percentage of individuals is exposed. The decision to integrate the probability from 0 to 100 hours is subjective. The optimal strategy for this criterion is determined by solving the following optimization problem:

$$\arg \sup_{\substack{a_0 \geq 0, \dots, a_{23} \geq 0 \\ \sum_k a_k = 1}} AUC_{PTA}(a_0, \dots, a_{23}). \tag{9}$$

The formulation for optimizing the multi-day cumulative strategy is analogous.

The formal definition of the first three criteria, as well as the optimization problem to be solved, is detailed in the Supplementary Material, section 2.

Results

Figure 1 presents the raw data on piglet water consumption over 35 days post-weaning. Each gray point depicts the amount of water either ingested or wasted by a piglet on a specific day. Additionally, the median of the T_i functions, obtained by fitting the model in Eq. 1 to the individual piglet data, is shown as a red line. The figure demonstrates that median water consumption increases over time (and with weight). Moreover, significant

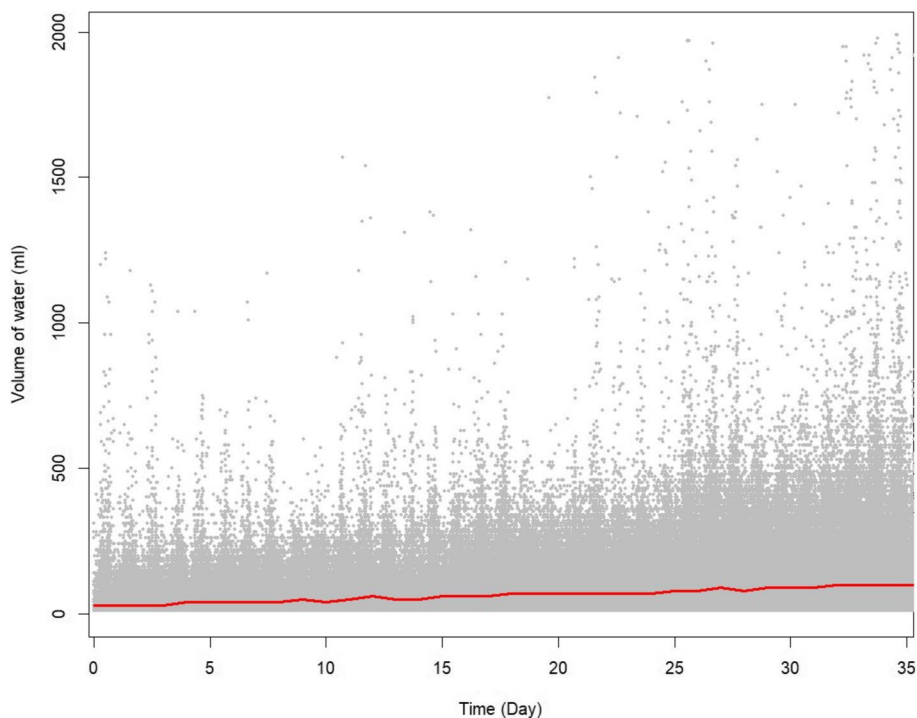


Fig. 1 Water consumption (in millilitres) of all piglets during the 35 days post-weaning. Each gray point represents the volume of water consumed by a piglet on a specific day. The red line shows the median of the functions T_i defined in Eq. 1

variability in the recorded water volumes is evident. However, the graph does not provide information on the density of data points corresponding to the percentage of piglets with low water intake, and consequently, lower exposure.

If for each piglet i , T_i is removed from Q_{ik} , it is obtained $P_i(t_{ik}) + \varepsilon_{ik}$, which contains information about 24-hour periodicity of the drinking behaviour. Figure 2 presents, as gray lines, the 24-hour segments of $P_i(t_{ik}) + \varepsilon_{ik}$ for all the individuals, plotted as a function of the hours in a day. The high variability observed at specific times can be attributed to differences in water consumption between animals and variations in the water intake of the same animal at that specific time across different days. Conversely, low variability at a given time suggests that, regardless of the day, all the animals display similar drinking behaviour during that period. This plot reveals that from 7:00 to 19:00, the variability in water consumption is lower than during the period from 19:00 to 7:00. Additionally, during the 7:00 to 19:00 period, the median, the 80th percentile and the 90th percentile display local maxima, indicating that most animals drink more water around noon and again around 17:00.

For the results related to the computation of optimal strategies, only a subset concerning amoxicillin is presented in the main text. The additional findings

related to doxycycline are provided in the Supplementary Material (Figures S1-S9). Figures 3, 4 and 5 display the optimal value achieved for the criteria 1, 2 and 3, respectively, as a function of the days post-weaning for each distribution strategy (i.e., usual, daily-fractionated, and multi-day cumulative).

Figure 3 shows that with the usual strategy, the minimum AUC remains below 1 mg.h/l, regardless of the day the treatment begins. In contrast, the minimum AUC is consistently above 1 mg.h/l, reaching up to 3 mg.h/l depending of the treatment start day when using the daily-fractionated strategy. Finally, the multi-day cumulative strategy ensures that all piglets achieve an AUC greater than 2.3-2.5 mg.h/l, irrespective of the treatment start day.

Figure 4 illustrates that, according to the second criterion, with the usual strategy, 95% of piglets will have an average AUC over 5 days approximately above 2 mg.h/l. This lower limit increases to 4 mg.h/l when using the multi-day cumulative strategy.

Finally, for the third criterion, Fig. 5 illustrates that, as anticipated, the multi-day cumulative strategy results in a lower CV compared to both the daily-fractionated and the usual strategies. Interpreting the CV in terms of individual exposure can still be challenging.

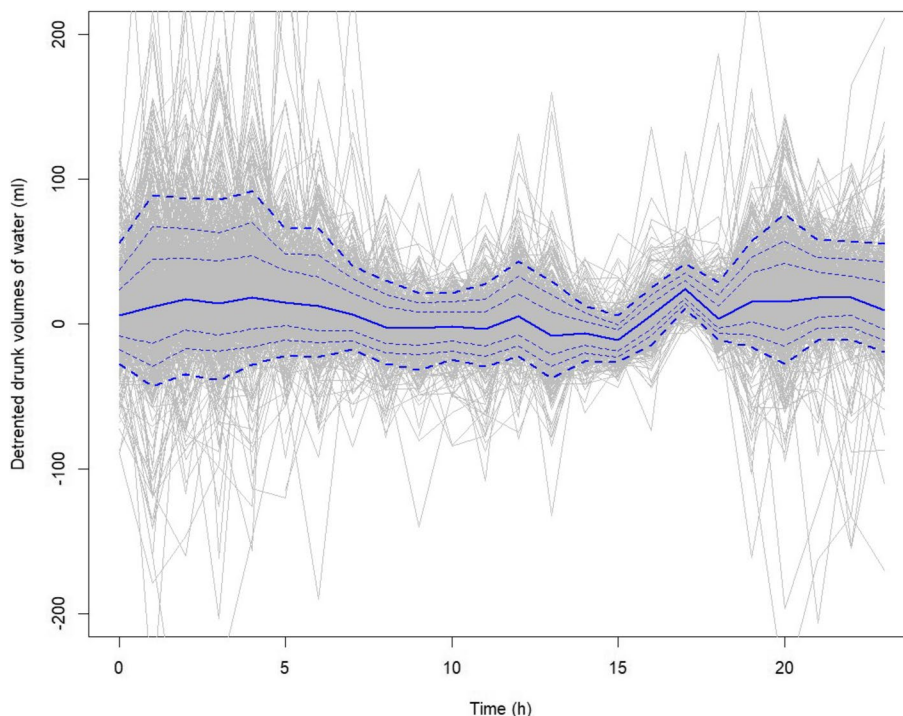


Fig. 2 For each individual i , the quantity $Q_{ik} - T_i(t_{ik}) = P_i(t_{ik}) + \varepsilon_{ik}$ is represented as a gray line, plotted as a function of the time of day. The blue curves correspond to the 5th, 10th, 20th, 50th, 80th, 90th and 95th quantiles

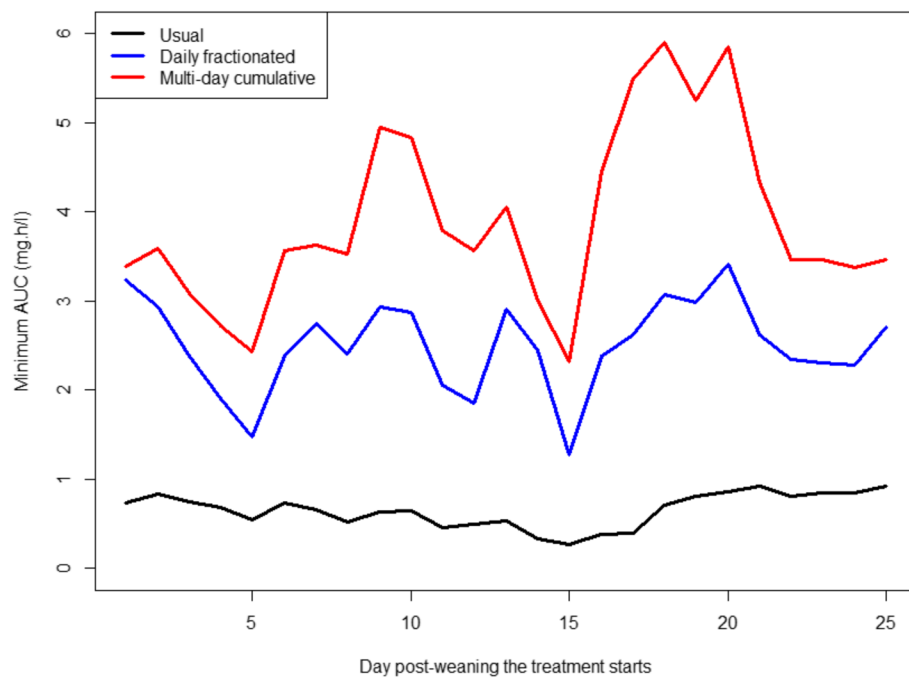


Fig. 3 Optimal value of criterion 1 (Minimum AUC) as a function of the days post-weaning when the treatment begins for each of the three drug distribution strategies: usual (black line), daily-fractionated (blue line) and multi-day cumulative (red line). Results correspond to amoxicillin

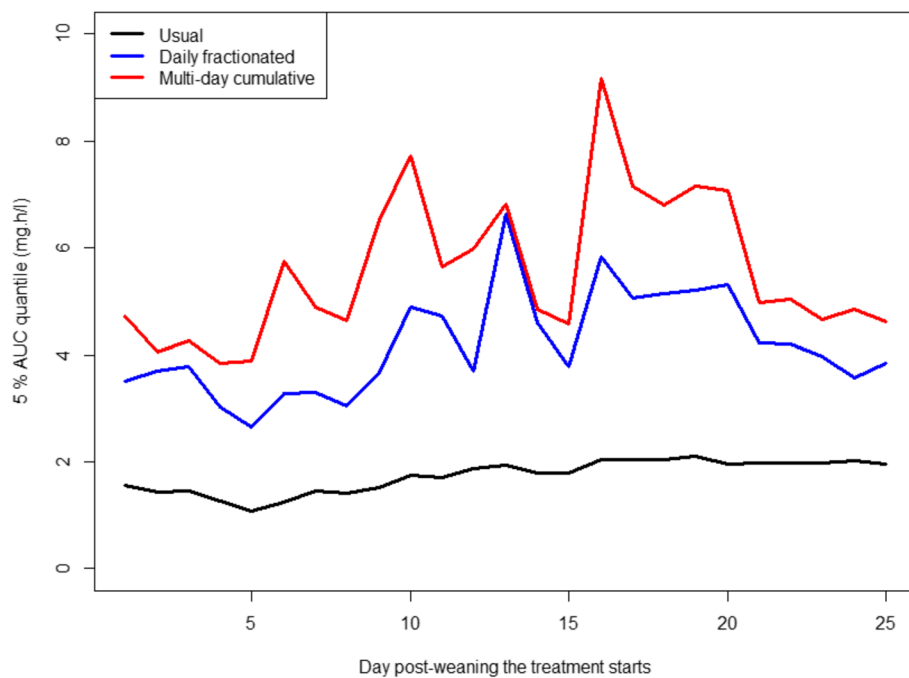


Fig. 4 Optimal value of criterion 2 (5th percentile of AUC) as a function of the days post-weaning when the treatment starts, for each of the three drug distribution strategies: usual (black line), daily-fractionated (blue line), and multi-day cumulative (red line). This calculation corresponds to amoxicillin

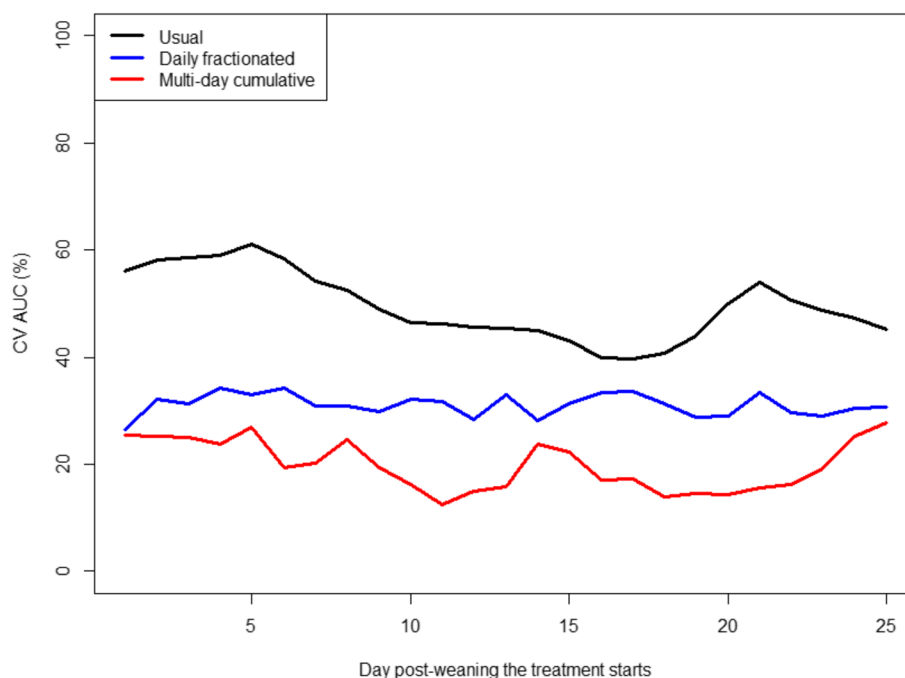


Fig. 5 Optimal value of criterion 3 (inverse of the coefficient of variation of AUC) as a function of the days post-weaning the treatment starts, for each of the three drug distribution strategies: usual (black line), daily-fractionated (blue line), and multi-day cumulative (red line). This computation corresponds to amoxicillin

Figure 6 shows the results concerning the optimization of criterion 4, which involves computing the area under the Probability of Target Attainment (PTA) curve. Panel (A) presents the PTA curves obtained using the MICs of *Pasteurella multocida*, while panel (B) displays the PTA curves obtained using the MICs of *Actinobacillus pleuropneumoniae*.

Both, Fig. 6A and B contains two panels. The left panel compares the PTA curves obtained using the usual strategy with those obtained using the day-fractionated strategy. The right panel compares the PTA curves obtained using the usual strategy with those obtained using the multi-day cumulative strategy.

In both figures, the PTA curves from the usual strategy are depicted as solid black lines, with one line corresponding each day when the treatment begins. The PTA curves from the day-fractionated and multi-day cumulative strategies are shown as dashed lines, with each line also representing the day when the treatment starts.

It can be observed that there is no dispersion between the PTA curves obtained using the usual delivery strategy. Regardless of the day post-weaning when the treatment begins, most piglets experience similar levels of under-exposure. In contrast, there is significant variability in the PTA curves depending on the day the treatment is initiated when the drug delivery is optimized. In all

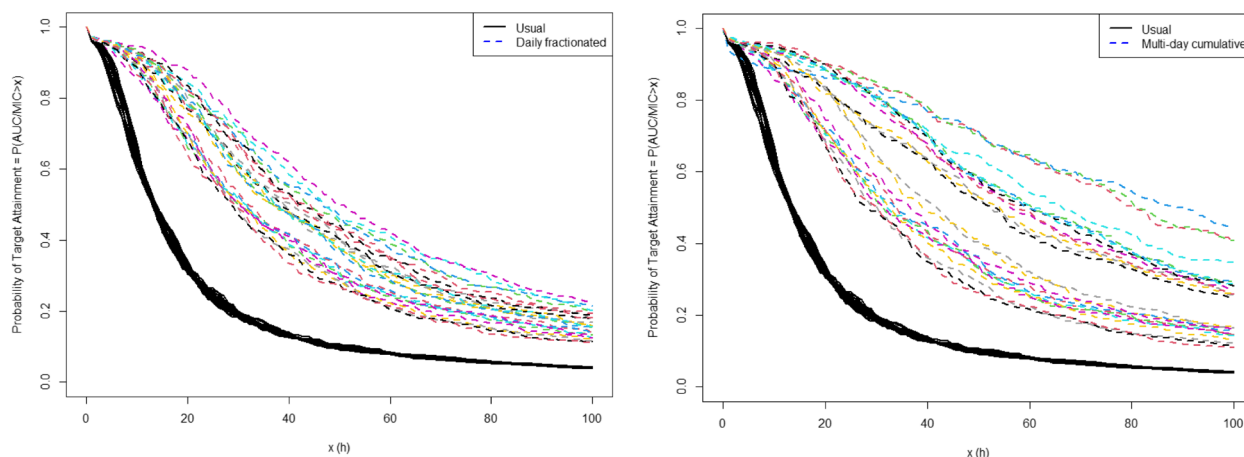
the cases, the PTA curve after optimization consistently exceeds the PTA curve obtained with the usual strategy, irrespective of the starting day of treatment.

The result of the optimization problem for the daily-fractionated strategy, using the PTAs computed with the MICs of *Pasteurella multocida*, is shown in Fig. 7. This figure illustrates the distribution percentages of the daily dose to be mixed into drinking water as a function of the time of day and the number of days post-weaning when the treatment begins. For example, if the treatment starts 6 days post-weaning, 23% of the daily dose should be added to the water provided between 15:00 and 16:00, while the remaining 77% should be dissolved in the water given between 16:00 and 17:00. No medication should be administered during times not shown in the figure.

This figure illustrates that, regardless of the day the treatment begins, the optimal time range for administering amoxicillin to achieve the maximum AUC of the PTA with *Pasteurella multocida* is between 15:00 and 18:00.

Figure 8 displays the ratio of the area under the PTA curve achieved with the daily-fractionated strategy to the area under the curve obtained with the usual strategy, as a function of the day the treatment begins. A ratio equal to 2 indicates that the area under the PTA curve with optimization is twice that without optimization.

A PTAs computed with the MICs of *Pasteurella multocida*



B PTAs computed with the MICs of *Actinobacillus pleuropneumoniae*

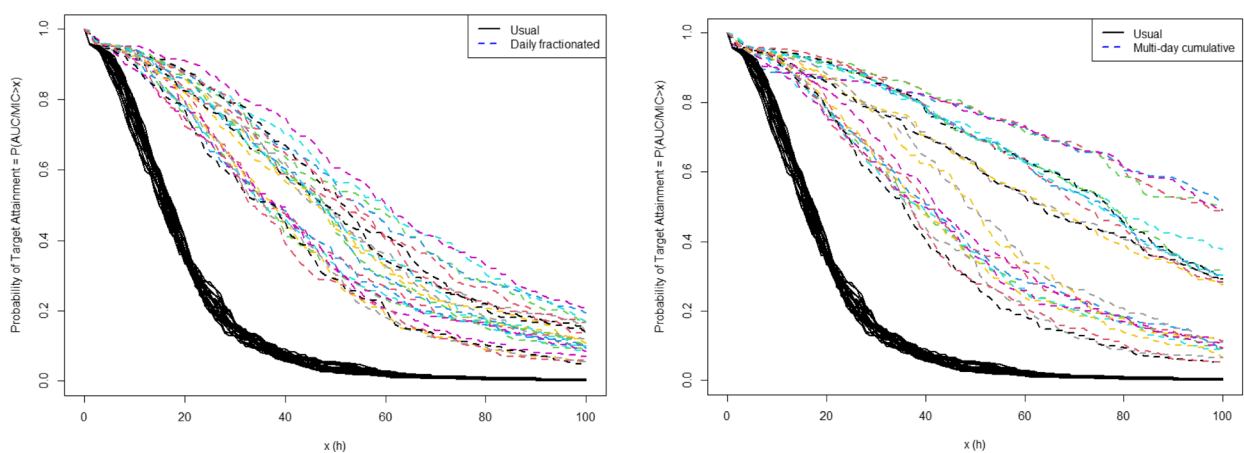


Fig. 6 **A** Probability of target attainment (PTA) as a function of hours, computed using the MICs of *Pasteurella multocida*. Both panels display the PTA curves obtained with the usual strategy (black solid lines). The left panel also shows the PTA curves for the daily-fractionated strategy (dashed lines), while the right panel also shows the PTA curves for the multi-day cumulative strategy (dashed lines). Each curve represents a different starting day for the treatment. **B** Probability of target attainment as a function of hours, computed using the MICs of *Actinobacillus pleuropneumoniae*. Both panels display the PTA curves obtained with the usual strategy (black solid lines). The left panel also shows the PTA curves for the daily-fractionated strategy (dashed lines), and the right panel also shows the PTA curves for the multi-day cumulative strategy (dashed lines). Each curve correspond to a different starting day for the treatment

This graph shows that optimization approximately doubles the area under the PTA curve, increasing it from 1.7 to 2.6. However, the extent of this improvement varies depending on the day the treatment begins. Specifically, when the treatment starts either less than 8 days post-weaning or at least 20 days post-weaning, the increase in the area under the PTA curve is about 2. The improvement can exceed 2.5 when the treatment starts 13 days post-weaning.

The result of the optimization problem using the multi-day cumulative strategy, with PTAs computed from the MICs of *Pasteurella multocida* is illustrated in Fig. 9.

Each plot in the figure represents the optimal distribution of the dose over the 120 hours (5 days) of treatment, corresponding to different starting days. Unlike the daily-fractionated strategy, the multi-day cumulative strategy optimizes the percentage of the total dose to be distributed across the 5 days of treatment.

Discussion

This article demonstrates that improving the general exposure of a group of pigs can be achieved by adapting drug delivery to their drinking behavior.

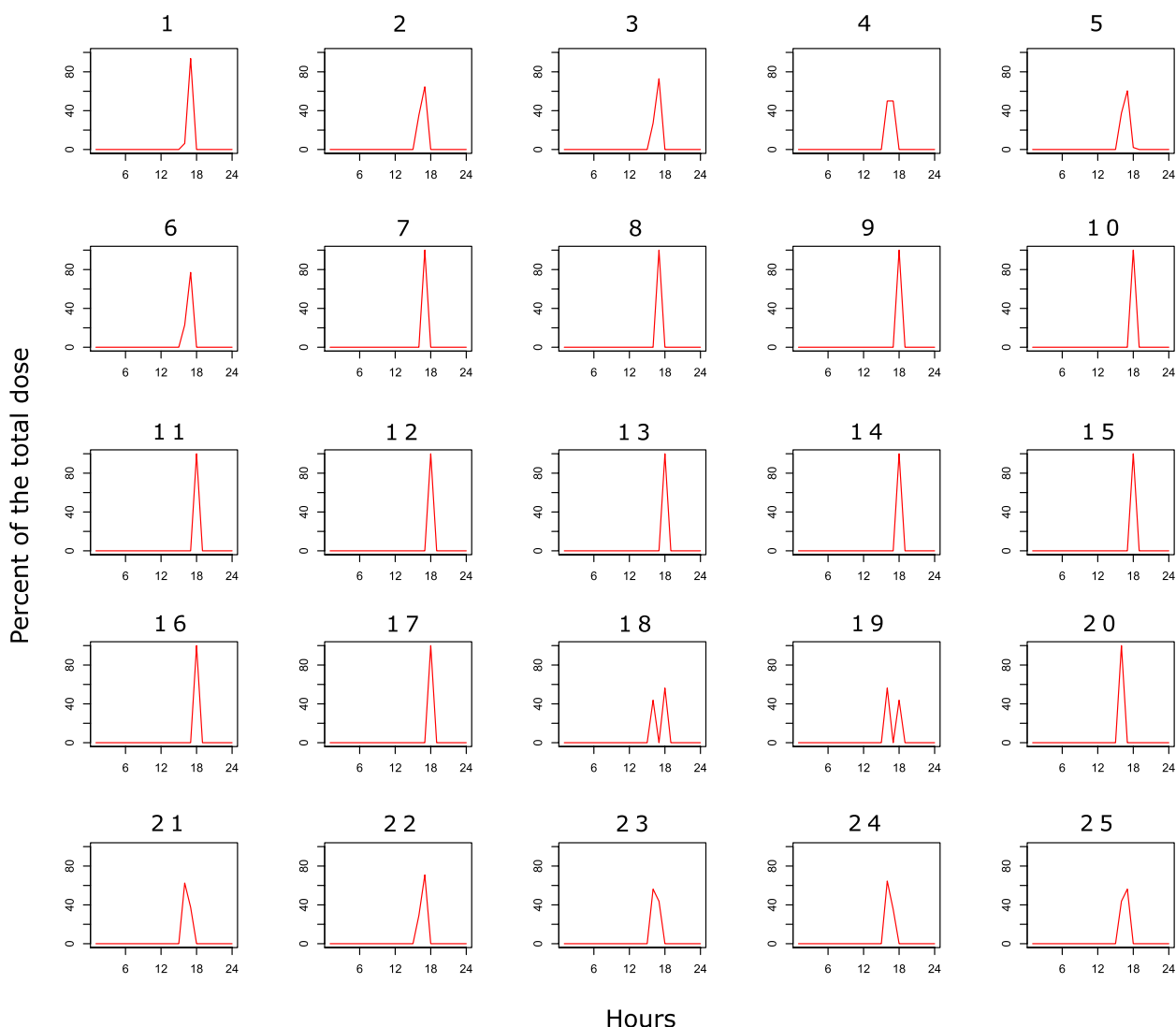


Fig. 7 Percentage of daily dose of amoxicillin to be delivered as a function of the time of day for each starting day of treatment, according to the daily-fractionated strategy, when optimizing criterion 4 using the MICs of *Pasteurella multocida*

Husbandry conditions have a significant impact on pigs’ drinking behavior. Factors such as temperature, light exposure duration and intensity, food type and quality, feeding schedules, pen space, and social interactions with litter mates and other piglets can influence their circadian rhythm and cause stress or aggressive behavior. External factors, including ventilation, air quality, and sudden noises, can also contribute to stress and anxiety in piglets [16–20].

Given these varied influences, the optimal strategies identified in this article are specific to the studied conditions and may not be directly applicable to other breeds. Calibration according to specific husbandry conditions is essential for effective implementation of the approach.

While calibration is required to adapt the strategy to individual farm conditions, it does not limit the applicability of the findings. The methodology introduced in this article provides a framework for farmers to develop an optimal distribution strategy tailored to their unique conditions, regardless of breed or genetic hybrid. For instance, installing a few connected water dispensers on sufficiently large farms could help assess whether the drinking behavior of the pigs aligns with the patterns observed in this study. Also, by collecting similar data, farmers can adjust the study’s conclusions to better fit their conditions, thus enhancing the applicability of the proposed method across different breeds and husbandry practices.

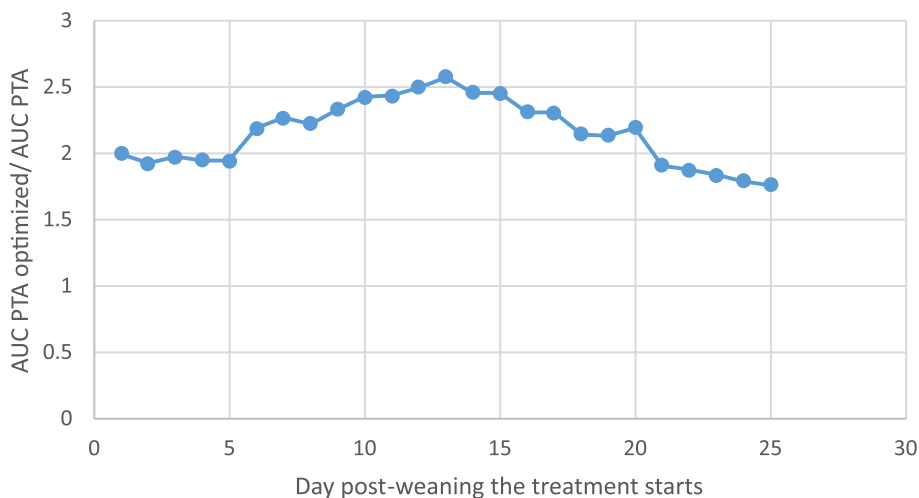


Fig. 8 Ratio of the area under the PTA curve achieved with the daily-fractionated strategy, using the MICs of *Pasteurella multocida*, as a function of the day the treatment starts

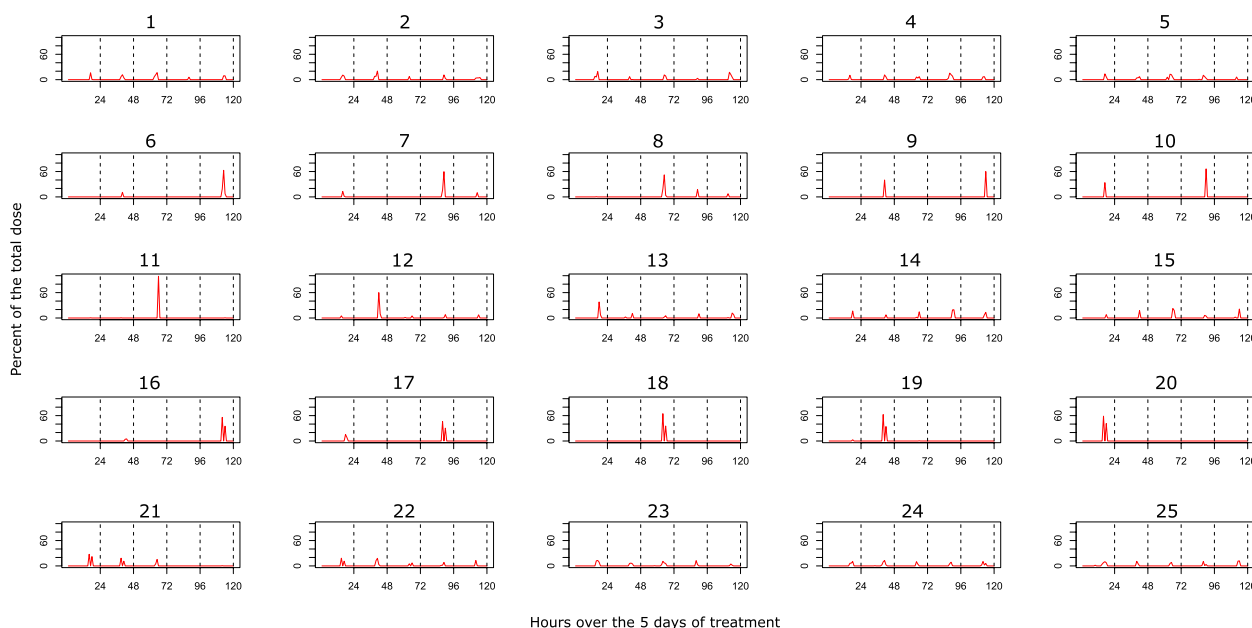


Fig. 9 Percentage of dose of amoxicillin to be delivered as a function of hours, according to the multi-day cumulative strategy, when criterion 4 is optimized using the MICs of *Pasteurella multocida*. Each plot corresponds to a different day post-weaning when the treatment starts. The vertical lines mark the end of each day of treatment

However, even with these initial considerations, it becomes evident that the conventional antimicrobial distribution strategy, referred to in this article as the usual strategy, appears to be among the least effective at first glance, despite its straightforward implementation. Labeling it as “the least effective” indicates that any modification to this strategy results in improved exposure of the animals to the medication.

A model for pig water consumption was introduced to address the existence of high water consumption values that do not align with the actual amount of water ingested by the animals. This empirical model avoids relying on the general rule of thumb that piglets drink roughly 10% (and never more than 20%) of their body weight daily. Instead, the model aims to describe “roughly” the animal drinking behaviour. A classical time series decomposition framework was used, breaking down the series

into its core components: trend, seasonal variation, and residuals. While more sophisticated models for water consumption exist in the literature [21, 22], the choice of this model is secondary to the paper's primary focus and has minimal impact, if any, on the results. Specifically, the criteria examined (except for criterion 3) are based on the lowest quantiles of the water consumption distribution. Therefore, these criteria are robust to outlier maximum value and rely on piglets with lower water intake, who experience reduced medication exposure.

Four criteria were proposed to determine optimal antimicrobial distribution strategies: minimum AUC, 5% quantile of AUC, inverse of CV, and AUC of PTA for a given bacterium. This list of criteria is not exhaustive, and other criteria could also be considered.

Once the responsible bacteria causing the infection are identified, using the Area Under the Curve (AUC) of Probability of Target Attainment (PTA) for that specific bacterium becomes the most suitable criterion. PTA allows the calculation of the percentage of individuals with an AUC/MIC exceeding the pharmacokinetic-pharmacodynamic cut-off [23]. Conversely, when the bacteria are not identified, the 5th quantile of AUC proves to be a more robust criterion, as it is less affected by unreasonably high water consumption and is straightforward to implement. Another potential approach could involve defining a criterion related to probabilistic antibiotherapy, which would rely on the prevalence of various bacterial families in the specific breeding context under consideration.

In addition to the criteria introduced, two types of strategies for modeling antimicrobial delivery throughout the treatment were proposed: the daily-fractionated strategy and the multi-day cumulative strategy. Our results indicate that the multi-day cumulative strategy generally offers greater exposure to the antimicrobial for the animals.

Overall, regardless of the chosen criterion and strategy, increasing the concentration of the antimicrobial in drinking water is essential when most (or ideally all) animals are drinking. While it is a common observation among pig farmers that pigs typically consume water around noon, the results from this study suggest that distributing antimicrobials at this time may not always be optimal, suggesting other hours for its distribution. This is because, although many animals drink water around noon, their individual drinking times can vary significantly, leading to a lack of collective synchronization. Thus, the optimal timing for antimicrobial distribution may differ and should be adjusted based on specific drinking patterns.

When applying the daily-fractionated strategy, where the same antimicrobial distribution pattern is maintained throughout the treatment days, it appears beneficial to

administer the antimicrobial between 15:00 and 18:00 (for both amoxicillin and doxycycline). This finding is consistent across all criteria (see Figures S10-S12 in the Supplementary Material for the optimal distribution patterns obtained using criteria 1, 2, and 3). Furthermore, the optimal times selected remain relatively stable regardless of the day post-weaning the treatment begins.

When utilizing the multi-day cumulative strategy, where a single antimicrobial distribution pattern is chosen across the 120 hours of treatment, the pattern varies depending on the treatment start day. For some treatment start days (e.g., days 1, 2, 3, 4, 5, 14, 15, 22, 23, 24, 25), the optimal multi-day cumulative strategy closely resembles the daily-fractionated strategy, with a nearly identical antimicrobial distribution pattern across all treatment days. However, for other treatment start days (e.g., days 6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 19, 20), the optimal strategy involves administering the entire dose within one or two days of the five-day treatment period. Notably, on all of these days, the optimal strategy suggests concentrating the medication on day 10, 13, or 20, indicating that subtle changes in farm management practices may have influenced piglets' dipsic behavior on these days. Although the cause of this regime shift is not fully understood, further investigation is warranted to ensure consistently optimal multi-day cumulative strategies, regardless of the treatment start day.

Implementing the multi-day cumulative strategy may also present practical challenges. This approach assumes that the amount of drug reaching the drinking trough aligns with the expected amount, which necessitates good solubility, stability of the antimicrobial, and low adsorption to the pipe [4, 24].

Given the substantial anticipated benefits, potentially doubling the optimized criteria, it seems more prudent to explore the fundamental factors influencing dipsic behavior further.

All our calculations are based on the empirical cumulative distribution functions of the AUC at each time point. With a sample size of approximately 1000 piglets, this approximation is highly accurate, and the presented statistics are subject to minimal sampling variability. Therefore, the sometimes erratic nature of the curves presented in the Figs. 3, 4 and 5 cannot be attributed to sampling variability. They are likely attributable to deterministic changes in drinking behaviour (which cause a change in the distribution).

In conclusion, our findings emphasize that the conventional approach of administering antimicrobials via drinking water is suboptimal. This article presents a methodology that enables farms to enhance animal exposure to antimicrobials without increasing overall usage,

based on a preliminary study characterizing the animals' drinking behavior.

The experimental design of this study did not account for certain water-related factors such as water quality (hardness and pH), water pressure in drinking lines, and the length of these lines. From a clinical perspective, these parameters can influence the variability of exposure among animals by affecting the availability of the active ingredient in the bowl drinkers.

All the outcomes stem from conducting group treatments, where identical concentrations of antimicrobial were maintained in the water for all animals. Individualizing the delivery of the drug could potentially enhance individual exposure, allowing for more precise dosing tailored to each animal's specific drinking behavior and needs. To individualize drug administration, it is necessary to predict the quantity of water each animal will drink on the next occasion. Some preliminary results (not presented in this article) suggest that such predictions are feasible. With these predictions, a dosing pump can be used to adjust the amount of drug administered at the next drink for each individual to achieve the target exposure. This approach ensures that each animal receives the exact dose needed, thereby improving treatment and avoiding the need to increase the drug quantity for the entire group, which should help reduce costs.

The economic value of individualization is challenging to document, as it depends on factors such as the price of the drug, its therapeutic index (i.e., the margin between effective and harmful doses), and the cost of the necessary equipment (e.g., dosing pumps). For a low-cost drug with a high therapeutic index, the economic benefits of individualization may be modest. However, this approach is particularly advantageous for expensive drugs with a low therapeutic index. This approach is analogous to Therapeutic Drug Monitoring, used in human medicine for drugs with a low therapeutic index, as it closely aligns with constructing individual parameter estimates derived from population pharmacokinetic models.

Supplementary Information

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Supplementary Material 1

Author' contributions

D.C. proposed the methodology. N.H. and D.C. performed the analyses. N.H., D.C., B.R., and M.L. drafted the paper. All authors critically reviewed several drafts and approved the final manuscript.

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Data availability

The data used in this study can be obtained upon request from the corresponding author. This data are not publicly accessible due to a confidentiality agreement.

Declarations

Ethics approval and consent to participate

The experimental protocol was authorized by the French Ministry of Research under the number 24958_2020032317345863. The animals used in our study were sourced from IFIP (Institut du Porc, Romillé, France). Since IFIP is a registered establishment authorized to use animals for scientific purposes, it was not necessary to obtain informed consent from individual owners. The project authorization was submitted to and approved by IFIP's ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

- Little S, Woodward A, Browning G, Billman-Jacobe H. In-water antibiotic dosing practices on pig farms. *Antibiotics*. 2021;10(2):169.
- Ferran AA, Roques BB. Can oral group medication be improved to reduce antimicrobial use? *Vet Rec*. 2019;185(13):402.
- Little S, Crabb H, Woodward A, Browning G, Billman-Jacobe H. Water medication of growing pigs: sources of between-animal variability in systemic exposure to antimicrobials. *Animal*. 2019;13(12):3031–40.
- Vandael F, de Carvalho Ferreira HC, Devreese M, Dewulf J, Daeseleire E, Eeckhout M, et al. Stability, homogeneity and carry-over of amoxicillin, doxycycline, florfenicol and flubendazole in medicated feed and drinking water on 24 pig farms. *Antibiotics*. 2020;9(9):563.
- Chassan M, Hémonic A, Concordet D. What matters in piglets' exposure to antibiotics administered through drinking water? *Antibiotics*. 2021;10(9):1067.
- Ferran AA, Lacroix MZ, Bousquet-Mélou A, Duhil I, Roques BB. Levers to improve antibiotic treatment of lambs via drinking water in sheep fattening houses: the example of the sulfadimethoxine/trimethoprim combination. *Antibiotics*. 2020;9(9):561.
- Kendall M. *Time Series*. 2nd ed. London and High Wycombe: Charles Griffin and Co Ltd.; 1976.
- Montgomery DC, Jennings CL, Kulahci M. *Introduction to time series analysis and forecasting*. John Wiley & Sons; 2015.
- Rey JF, Laffont CM, Croubels S, De Backer P, Zemirline C, Bousquet E, et al. Use of Monte Carlo simulation to determine pharmacodynamic cutoffs of amoxicillin to establish a breakpoint for antimicrobial susceptibility testing in pigs. *Am J Vet Res*. 2014;75(2):124–31.
- Del Castillo J, Laroute V, Pommier P, Zemirline C, Keïta A, Concordet D, et al. Interindividual variability in plasma concentrations after systemic exposure of swine to dietary doxycycline supplied with and without paracetamol: a population pharmacokinetic approach. *J Anim Sci*. 2006;84(11):3155–66.
- European Committee on Antimicrobial Susceptibility Testing. Data from the EUCAST MIC distribution website, last accessed 5 June 2024. <https://www.eucast.org>.
- Kahlmeter G, Turnidge J. How to: ECOFFs—the why, the how, and the don'ts of EUCAST epidemiological cutoff values. *Clin Microbiol Infect*. 2022;28(7):952–4.

13. Ambrose PG, Grasela DM. The use of Monte Carlo simulation to examine pharmacodynamic variance of drugs: fluoroquinolone pharmacodynamics against *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis*. 2000;38(3):151–7.
14. Lees P, Pelligand L, Illambas J, Potter T, Lacroix M, Rycroft A, et al. Pharmacokinetic/pharmacodynamic integration and modelling of amoxicillin for the calf pathogens *Mannheimia haemolytica* and *Pasteurella multocida*. *J Vet Pharmacol Ther*. 2015;38(5):457–70.
15. Andes D, Craig WA. Pharmacokinetics and Pharmacodynamics of Tetracyclines. in *Antimicrobial Pharmacodynamics in Theory and Clinical Practice*. CRC Press, 2007, pp. 279-290. <https://www.taylorfrancis.com/chapters/edit/10.3109/9781420017137-16/pharmacokinetics-pharmacodynamic-tetracyclines-dave-andes-william-craig>.
16. Pijpers A, Schoevers E, Van Gogh H, van Leengoed L, Visser I, van Miert A, et al. The influence of disease on feed and water consumption and on pharmacokinetics of orally administered oxytetracycline in pigs. *J Anim Sci*. 1991;69(7):2947–54.
17. Seddon Y, Farrow M, Guy J, Edwards S. Can monitoring water consumption at pen level detect changes in health and welfare in small groups of pigs. In: *Proceedings of the 5th International Conference on the Assessment of Animal Welfare at Farm and Group Level*. Ontario; 2011. pp. 8–11.
18. Turner S, Edwards S, Bland V. The influence of drinker allocation and group size on the drinking behaviour, welfare and production of growing pigs. *Anim Sci*. 1999;68(4):617–24.
19. Mroz Z, Jongbloed AW, Lenis NP, Vreman K. Water in pig nutrition: physiology, allowances and environmental implications. *Nutr Res Rev*. 1995;8(1):137–64.
20. Vermeer HM, Kuyken N, Spooler HA. Motivation for additional water use of growing-finishing pigs. *Livest Sci*. 2009;124(1–3):112–8.
21. Madsen TN, Kristensen AR. A model for monitoring the condition of young pigs by their drinking behaviour. *Comput Electron Agric*. 2005;48(2):138–54. <https://doi.org/10.1016/j.compag.2005.02.014>.
22. Bus JD, Boumans IJ, Engel J, Te Beest DE, Webb LE, Bokkers EA. Circadian rhythms and diurnal patterns in the feed intake behaviour of growing-finishing pigs. *Sci Rep*. 2023;13(1):16021.
23. Toutain PL, Sidhu PK, Lees P, Rassouli A, Pelligand L. VetCAST method for determination of the pharmacokinetic-pharmacodynamic cut-off values of a long-acting formulation of florfenicol to support clinical breakpoints for florfenicol antimicrobial susceptibility testing in cattle. *Front Microbiol*. 2019;10:1310.
24. Georgaki D, Vandael F, Cardoso de Carvalho Ferreira H, Filippitzi ME, De Backer P, Devreese M, et al. Qualitative risk assessment of homogeneity, stability, and residual concentrations of antimicrobials in medicated feed and drinking water in pig rearing. *BMC Vet Res*. 2023;19(1):1–12.

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