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JAC-Antimicrobial Resistance

Economic evaluation of antimicrobial use practices in animal agriculture: a case of poultry farming

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Background: The growing evidence of the contribution of antimicrobial use (AMU) in animal agriculture to the public health threat of antimicrobial resistance has highlighted to policymakers the importance of the need for prudent AMU in animal production. Livestock farming is an economic process, where farmers are using inputs such as antimicrobials to minimize their losses.

Objectives: Using a large and unique dataset combining time-series data on economic performance and health records in conventional broiler production in France, we identify how improved healthcare management and disease prevention impact economic performance, AMU reduction and health outcomes.

Methods: We analyse the main characteristics of the economic performance of farms measured by the profit per m^2, by performing advanced regression models investigating the relative importance of medication and veterinary procedures.

Results: In our study, 50% of the treatments (expressed as number of new treatments) are attributable to only 30% of all flocks. There is an inverted U-shaped relationship between AMU and economic performance. This finding implies that the marginal profit of antimicrobials is decreasing, meaning that using antimicrobials is only profitable up to a certain threshold. Results also show that the profit increases as the number of preventive treatments increase.

Conclusions: Our findings suggest that policies encouraging farmers to work upstream from the occurrence of disease have the potential to perform better than regulations, as they would maintain a profitable activity while diminishing AMU. Encouraging adequate infection control practices by subsidizing or providing other incentives would benefit farmers and society.

Introduction

The global burden of antimicrobial resistance (AMR) is not new, yet its magnitude may inhibit our ability to control even simple bacterial diseases infecting patients without comorbidity. In the USA, the total costs of AMR are estimated to be USD2.2 billion (€2.2 billion) in 2014.[1] In Europe, AMR costs are estimated to be €1.5 billion (USD1.5 billion) per year in healthcare costs and productivity losses.[2] The fight against AMR involves a wide variety of measures, spanning from strengthening the antimicrobial pipeline to improving use practices. Millions of dollars have been invested to win the race against resistance by making new antimicrobials available. The Organisation for Economic Co-operation and Development (OECD) estimates that USD547 million has been invested to support the preclinical development of antimicrobials and other AMR-related projects.[3] However, only a few such projects are in a development phase or have reached the market. In addition, the moderate return on investment and profitability of antimicrobial markets threatens the current availability of antimicrobials, as costs to maintain commercialization and remain compliant with the regulations may offset the benefits and threaten the overall development of substitute antimicrobials.[4] Besides, new molecules reaching the market would be classed as reserve drugs, and would be used as last resort for treating life-threatening pathogens in human patients only.

In the fight against AMR, a 'lower' hanging fruit and readily applicable strategy consists of reducing antimicrobial use (AMU). From an end-user point of view, reducing AMU has proven effective in reducing AMR in pathogens and commensal bacteria in both human and animal health, at least in some specific settings.[5]

Animal agriculture is an important sector of AMU. The burgeoning demand for animal protein, linked to the increasing size of the global human population and a shift in diet towards an increasingly animal protein-based diet, has generated an indirect increase in antimicrobials. Demand for animal-sourced foods is increasing in low- and middle-income countries, driven by population growth and higher standards of living.[3,6] This leads to an intensification of farming processes, sometimes accompanied by an increase in AMU if infection control measures are not well implemented.[7,8] Indeed, AMU in livestock is expected to double in Brazil, China, India, Russia and South Africa by 2030.[9] The worldwide increase of AMU in animal agriculture is projected to rise by 11% in 2030.[10] The quantitative relationship between AMU in agriculture and its impact on human health is not clear cut, yet there is strong policy pressure to reduce AMU in animal health.[3] Common healthcare management practices include preventing the occurrence of diseases, implementing biosecurity or vaccination programmes, referring to practitioners for an early and reliable diagnosis, and using diagnostic tools to ensure appropriate AMU.[4,11–13]

However, reducing AMU may come at a cost. A unique trait of AMU in animal agriculture is its drivers. As livestock farming is an economic process, where the outputs are the quantities of commodities sold, e.g. milk yield, eggs and kg of carcass, farmers use inputs to maximize their profit in the long run. Antimicrobials are generally affordable tools that help prevent and cure infectious diseases and offset economic risks and damage on a farm. From an individual perspective, only private costs and benefits are accounted for, meaning that the societal costs of AMR, i.e. the health and economic burden on public health, are not borne directly by farmers. Therefore, any strategy targeting decreasing AMU should also be profitable for farmers. Surprisingly, economic benefits associated with AMU, as well as the effects of options that could be substitutes for antimicrobials, have scarcely been studied. Using a large and unique dataset combining time-series data on economic performance and health records in conventional broiler production, we identify how improved healthcare management and disease prevention impact economic performance, AMU reduction and health outcomes. We hypothesize and test a non-linear, inverted U-shaped relationship between AMU and economic performance. Finally, we evaluate potential substitutions among infection control tools.

Materials and methods

Data description

In this study, the chosen epidemiological and statistical unit corresponded to the flock used in the sector, i.e. a group of chickens set up on the same date and in the same barn. All animals in the flock experience the same living and feeding conditions. All data were provided through the courtesy of a large veterinary practice in France representing 1086 flocks. More specifically, two main sources were exploited: (i) the main characteristics of the flocks with the economic performance of farms measured via the profit per m^2 were used as our dependent variable; and (ii) the veterinary prescriptions applied to these flocks. The variables related to the characteristics of flocks were the number of flocks (Nb_flocks), the weight of flocks at the slaughterhouse (Weight_flocks), the average age of flocks at the slaughterhouse (Average_age), the average daily gain (ADG), and the density, mortality and condemnation of the flocks as well as different indexes such as the performance index (IP), technical consumption index (ICT) and economical consumption index (ICE). We matched these two data sources over the period 2017–19. Notably, over the study period, a single farm is generally raising multiple flocks. To account for a potential farm effect, we tested the relationship between our variables at the flock and the farm level.

Economic modelling

Detailed information on the methods developed in this study is presented in the Supplementary Methodology S2, available as Supplementary data at *JAC-AMR* Online. To summarize, we first elaborated a statistical analysis to determine the characteristics of flocks according to the relative importance of veterinary practices. A Bonferroni correction was used (*P* values multiplied by 2 because the two *t*-tests were performed separately). Second, we analysed the main characteristics of the economic performance of farms measured by the profit per m^2. We performed a linear regression to highlight the determinants of economic performance. We considered this second part to be our baseline estimation scenario or benchmark. This characterization made it possible to better identify and enhance the contributions of AMU to the economic performance of the flocks. We also investigated the effect of vaccine use as a covariate. By way of robustness in our regression analysis, the significant main factors served as control variables when estimating the impact of veterinary medicines on economic performance. From this perspective, using regression analysis, we estimated a quadratic economic performance for France's poultry production according to AMU. We hypothesized and tested a non-linear relationship between AMU and economic performance.[14] The basic model is:

$$E_i = \alpha + \beta_1 Antimicrobials_i + \beta_2 Antimicrobials_i^2 + \delta Nbvaccinesi + \theta_k Xik + \varepsilon_i \quad (1)$$

where E_i denotes the economic performance (measured via the profit per m^2 on farm (i) and $Antimicrobials_i$ denotes the number of antimicrobial treatments during the fattening period. One treatment corresponds to either a single drug or a combination of drugs started on the same day, given a number of days set by the prescriber. $Nbvaccines_i$ represents the number of vaccines administered to the flocks and X_{ik} are the explanatory variables described above, which are meant to control the socioeconomic conditions in poultry production. An inverted-U curve path exists if there is a statistically significant relationship between AMU and economic performance.

An inverted U-shaped relationship between economic performance and AMU suggests that, empirically, an economy is associated with smaller levels of economic performance after some AMU threshold.

Regressions using instrumental variables (IV) method

Both profit and AMU could be driven by unobserved factors related to farmers' characteristics. The standard approach to deal with endogeneity in regression analysis is to use IVs. To correct for endogeneity, we constructed three different sets of instruments as follows: (i) information on disease prevalence, such as density and climatic conditions (period of rearing of flocks); (ii) medication information, e.g. age of treatment, and vaccine use; and (iii) other veterinary procedures (routine surveillance, necropsy, bacteriology and parasitology diagnostics, water analysis). According to the IV method, we performed a 'two-stage least squares' estimation. In the first equation, we estimated the factors that may explain AMU. We used this result to obtain the predicted value of

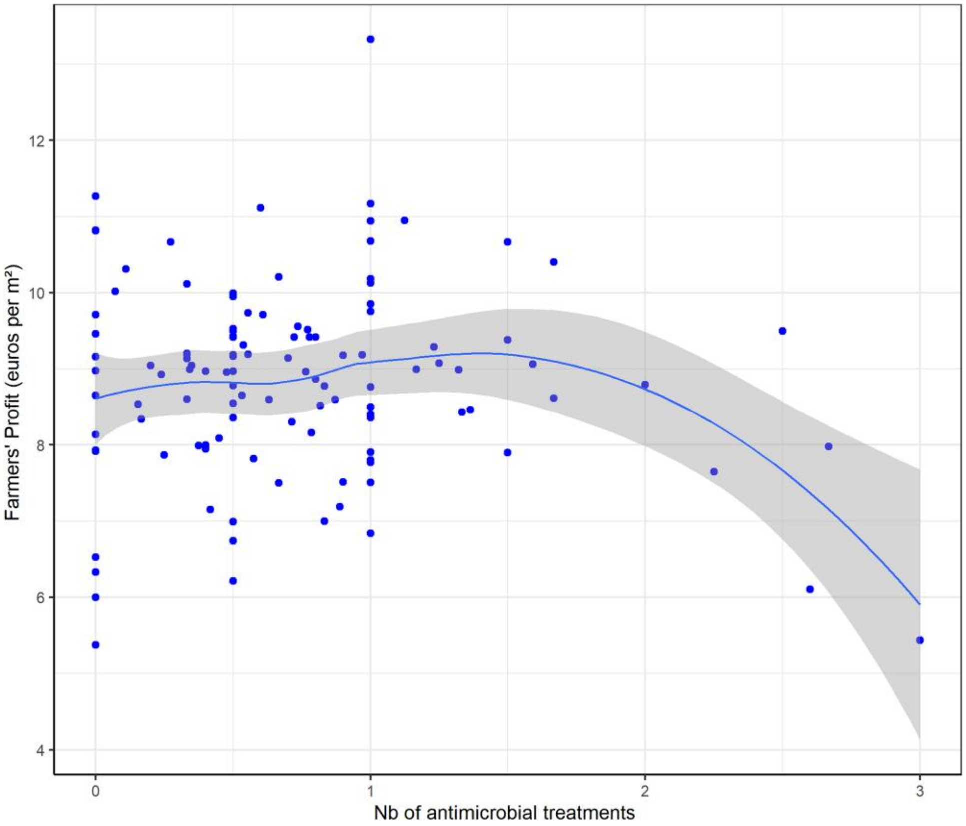

Figure 1. Profit according to the number of antimicrobial treatments, plotting the relationship between farmers' profit per m^2 and number of antimicrobial treatments at the farm level.

AMU. We then plugged the predicted value into the 'second-stage regression' to determine how the profit responds to the changes in AMUs that are driven by the instruments. Both to test robustness (with alternative indicators for AMU) and to interpret in terms of elasticity, we performed alternative regressions by linearizing our models.

Robustness checks

First, we performed ordinary least square (OLS) regressions to compare them with the IV results. The main results remained consistent (Table S2).

To assess the stability of our results, we also carried out our estimations on the basis of two criteria: (i) through the estimation method with the number of treatments; and (ii) via alternative indicators of AMU—animal course dose (ACD) and weight of active ingredient (WAI).

Alternative indicators were calculated as follows.[15–17] The ACD reflects the number of animals treated; it is calculated by dividing the amount of antimicrobials given in a batch (in mg) by the daily dose indicated by the veterinarian (in mg/kg), the duration of treatments (in days), and the weight at treatment (in kg). We estimated the weight at treatment as the date of treatment onset was available, as well as the average weight of animals at the beginning of the fattening period and their weight at harvest. The ACD was calculated for each active ingredient contained in each drug. The WAI (in mg), is deduced from the number of pharmaceutical units sold multiplied by the amount of active ingredient found in each drug.

From a qualitative point of view, we also considered the World Health Organization for Animal Health (WOAH) criteria for AMU.[18]

The veterinary critically important antimicrobial agents (VCIA) were broken into two tiers, based on their importance in human medicine. In our dataset, the VCIA tier 1 consisted of amoxicillin, ampicillin, phenoxymethylpenicillin, spectinomycin, sulfadiazine, trimethoprim and tylosin. The VCIA tier 2 consisted of enrofloxacin. The veterinary highly important antimicrobial agents (VHIA) in our dataset were colistin, flumequine and lincomycin. No veterinary important antimicrobial agents (VIA) were used in the flocks enrolled in our study.

Results

Descriptive statistics

The average profits are €8926 and €8994 per m^2 for farmers using zero or only one ACD, respectively, and these figures are not significantly different. Figures 1–3 show the observations profit per m^2 according to different AMU indicators at the farm scale.

We observe a clear difference in profit between farmers using zero treatment per flock and those using three or more, the latter having a drop in profit of 12.6% (Figure 4). Analysing the relationship between the profit and the class of antimicrobials used shows that farmers using antimicrobials of the VHIA category, such as colistin, perform less well than those not using antimicrobials (Figure 5). Generally, regardless of the indicator and the level of analysis (flock or farm), we observe that the profit first increases with AMU, before reaching a maximum where profit decreases with increased AMU.

The Lorentz curves (Figure 6) depict the cumulative importance of farms classified from the highest user to the lowest user in terms of the total number of uses in the population. The diagonal represents a population where the quantitative use of antimicrobials does not vary among individuals. Therefore, the

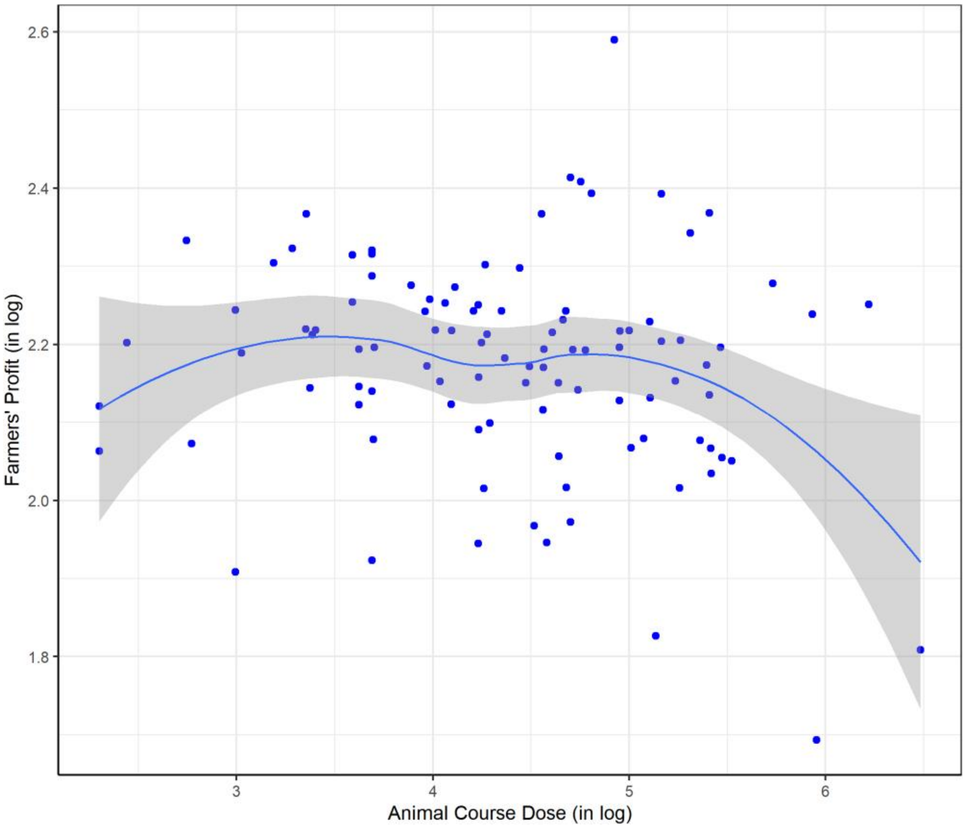

Figure 2. Profit according to ACD, plotting the relationship between farmers' profit per m^2 and animal course dose at the farm level after logarithmic transformation. Due to the existence of high variability for ACD, a logarithmic graph would highlight any substantial changes to the trend—whether upward or downward.

more the population curve deviates from it, the greater the disparities are in the use between farms. We observe that 50% of the number of antimicrobial treatments are attributable to only 30% of all flocks (325 flocks out of 1086).

The profit increases significantly, by 7.03% and 22.41%, when farmers vaccinate against two and three diseases, respectively (Figure 7). We do not observe any difference between the profits of farmers using veterinary diagnostics at a low level and those of farmers using such tests at a higher level.

Econometric results

First, we observe that the farmers' management style or the individual characteristics of the farmers positively affect the profit at the scale of the flocks (Table 1). Estimation results show that the inclusion (in columns 2 and 4) or absence (in columns 1 and 3) of the unobservable individual heterogeneity (i.e. farmer effects) do not affect the stability of econometric regressions.

Second, we observe that the number of antimicrobial treatments negatively impacts the profit of flocks, as shown in the results of the linear form (columns 1 and 2). The first two columns of Table 1 display a linear relationship analysis (columns 1 and 2, with and without fixed effects, respectively). This means that on average, a one-unit increase in number of treatments leads to a decrease of €2.0287 of profit for a given flock (column 1), all other things being equal. The quadratic form (columns 3 and 4, with and without farmer effects, respectively), sheds light on this decreasing trend. Indeed, we observe that only the antimicrobial treatments squared are negative. The turning points of these inverted U-shaped relationships vary for different indicators of AMU. Beyond this threshold, a one-unit increase (in number of treatments) leads to an average €2.29 per m^2 (i.e. 21.55%) reduction of profit (Figure S5). This result implies that heavy antimicrobial consumers are less efficient. Third, we observe that prevention, particularly the number of vaccines administered, has a positive impact on the profit of flocks, regardless of the model specification. An increase of one unit of vaccine leads to an average increase of €0.42 and €0.28 per m^2 (for linear and quadratic regressions, respectively). Finally, we observe that control variables linked to the flock characteristics (average age of removal flocks, average daily gain, and density of the flocks) are positive and significant. For example, an increase of one unit in the average age of flocks implies an increase of 15.71 cents per m^2 of profit. This result remains valid regardless of specifications.

Our robustness checks show that regardless of the specification form (linear or quadratic) and regardless of the indicator used (ACD or WAI), our main results remain valid (Table S2).

Discussion

Poultry production is the fastest growing agricultural subsector, especially in low- and middle-income countries. The global

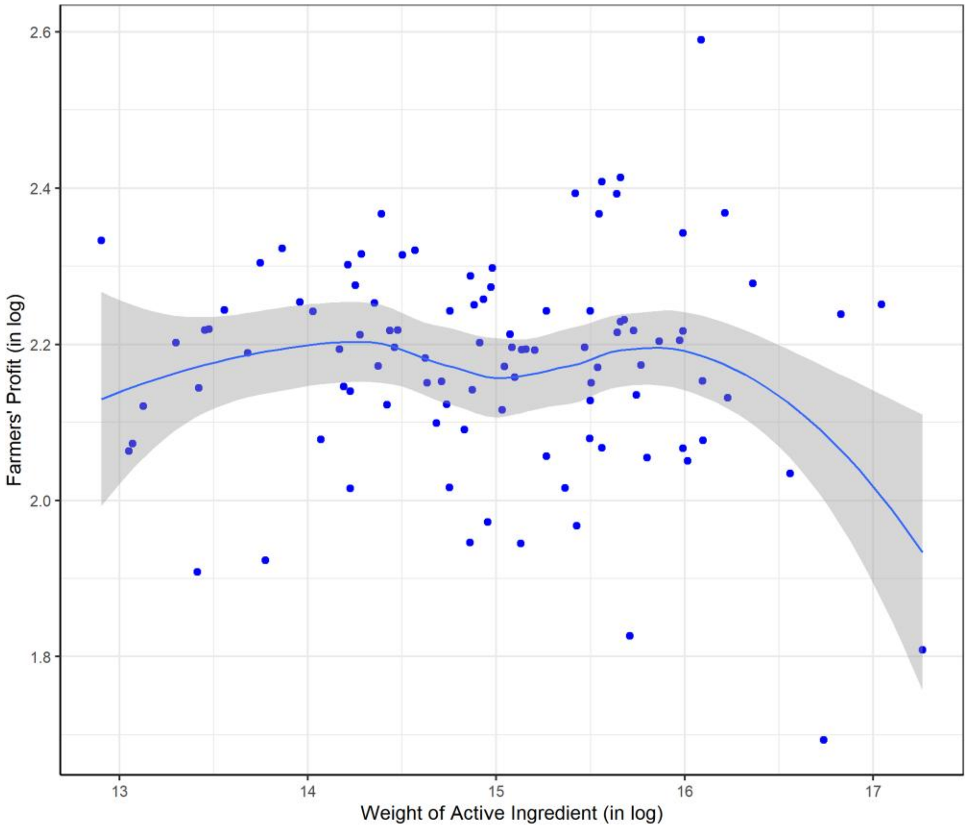

Figure 3. Profit according to the WAI indicator, plotting the relationship between farmers' profit per m^2 and number of AMU treatments at the farm level after logarithmic transformation. Due to the existence of high variability for WAI, a logarithmic graph would highlight any substantial changes to the trend—whether upward or downward.

poultry sector is expected to continue to grow as demand for meat and eggs is driven by growing populations, rising incomes and urbanization.[19] Genetic progress has given rise to birds that maximize feed efficiency utilization with shorter finishing periods but are generally more prone to diseases and require expert technical and healthcare management. The high level of integration of poultry production has led to an important standardization of the production process at a global level. This means that although our results represent only a subset of the global poultry production, the challenges faced by farmers engaged in conventional intensive production are fairly similar.

In our study, we observed an inverted U-shaped relationship between AMU and profit, which can be explained as follows. The increasing segment of the curve reflects the fact that there is a level of AMU that improves the economic performance of the flocks. This increasing part could be associated with required antimicrobial treatments, i.e. in a given production system, a certain quantity of antimicrobials is necessary to maintain animal health. The marginal benefit of AMU is higher than the marginal damage, which results in an increase in economic performance. By analogy, the decreasing segment refers to a situation in which the marginal damage outweighs the marginal benefit. Flocks using fewer antimicrobials perform better, which is likely associated with better control over hygiene, feeding and sanitation with such flocks. This finding is in line with a previous study, suggesting that compliance with biosecurity rules, particularly by changing clothes, shoes etc., is associated with lower AMU in broiler production.[20]

A major concern in veterinary pharmacoepidemiology is related to the quantification of AMU.[21] Indeed, there is no consensus on the best measure of AMU. In addition, choosing one indicator to the detriment of another can lead to divergent results. To overcome this situation, we evaluated the impact of AMU, considering both quantitative and qualitative considerations. Our main results remained robust with the three metrics.

The non-linear relationship observed between AMU and profit follows the theoretical forms of other production inputs in at least two ways. The marginal effect of AMU remains negative regardless of the econometric specification. This is consistent with the literature, where diminishing marginal rate of return is a very well-accepted economic fact.[22] In the production function literature, the squared form of input is often used to capture non-linear effects.[23,24] Notably, this result is also in line with the canonical environmental Kuznets curve (EKC) approach, tested in human health to analyse the relationship between vaccination rate and income, or in the case of agricultural pesticide use.[14,25,26] Our findings enable us to formulate some recommendations. First, there is a need to target heavy users with stewardship programmes, enabling them to decrease their AMU while improving animal health and subsequent profit. Second, stewardship

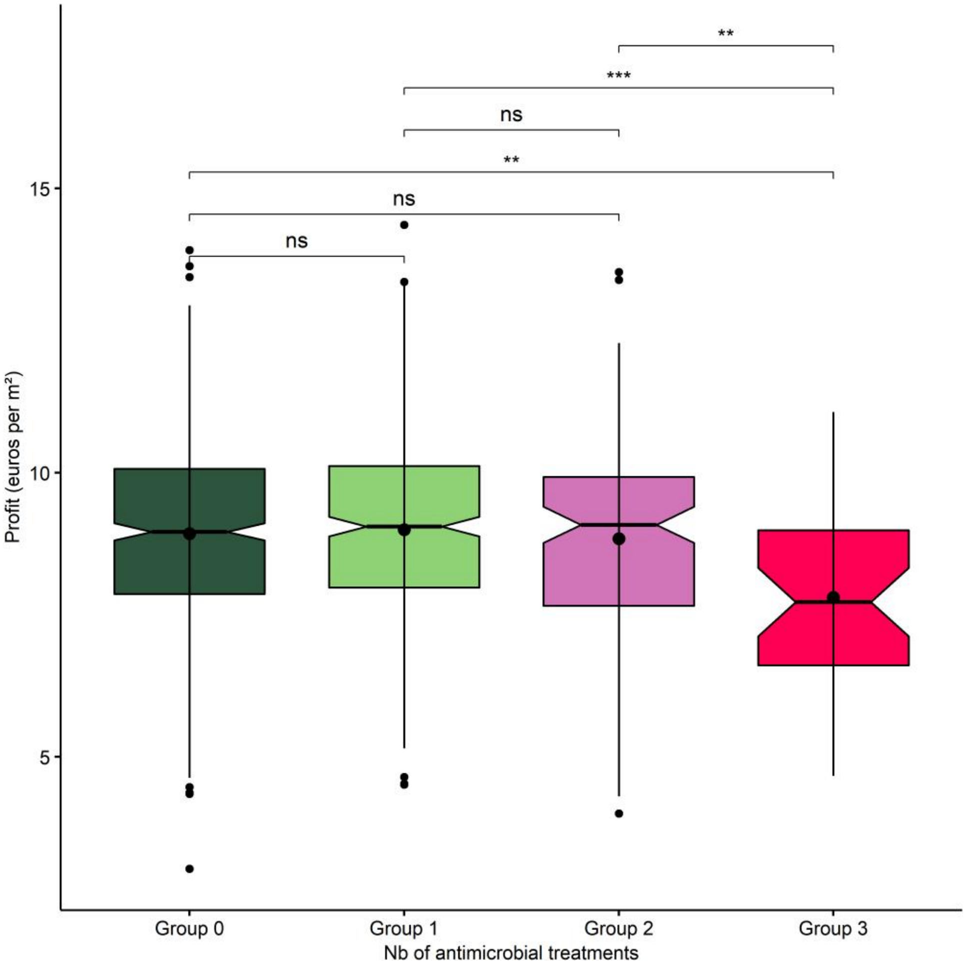

Figure 4. Relationship between economic performance and AMU, analysing the relationship between antimicrobial treatments and economic performance. Group 0 corresponds to flocks that did not use any antimicrobials. Groups 1, 2, 3 represent flocks that used 1 2, 3 or more antimicrobial treatments, respectively.

programmes could be developed to support 'low' antimicrobial users in a transition towards no use. Interestingly, it is likely that there is no such thing as 'one programme fits all' concerning stewardship, especially in this case. In our study, 55% of antimicrobial treatments are attributable to only 30% of all flocks.

Although the evaluation of risk factors for diseases and the behaviour of farmers was out of the scope of this study, these parameters do influence AMU and farm profit.[27] We observed that flocks with lower average daily gains were also high antimicrobial users. While improving hygiene and increasing disease prevention may prove useful to help transform 'high' users into 'moderate' users, as shown in our study, such a strategy may be less relevant than transforming 'one time' users into 'no' users. Indeed, the rationale for AMU may lie not in medical factors but in behaviours. For example, it has been shown that farmers' risk aversion influences farms' antimicrobial demands.[28]

In our study, the main drivers of profit in poultry were neither the intensity nor the category of antimicrobials. Indeed, economic performance depends first on the intrinsic characteristics of the farms, such as variables related to the weight of flocks at harvest.

In an effort to transition to minimal AMU in poultry, a set of policy instruments from regulations to economic incentives can be implemented. From a factual point of view, regulatory measures have already been implemented in several countries to supervise AMU under certain conditions, such as the ban on use for growth promotion (2006) in European countries and the ban on a certain class of antibiotics such as fluoroquinolones in the USA. Some scholars studied the economic impacts of these regulatory measures in the USA using simulation approaches, particularly (i) the prohibition of AMU;[29] (ii) antibiotic prohibition as a growth promoter in cattle, pigs and poultry;[30,31] and (iii) the prohibition of all usage in dairy cattle.[32] Regulations affecting AMU, such as intensity standards, supervision and the prohibition of the use of certain classes, are effective in reducing the use of antimicrobials. However, they may also impact on farmers' profits if there is a lack of substitute and technologies for antimicrobials. In Denmark, for example, a ban on antimicrobials for growth promotion decreased total AMU, but increased therapeutic use and raised production cost[33] in pork production. Denmark, Norway and Sweden reported that phasing out growth promotion led

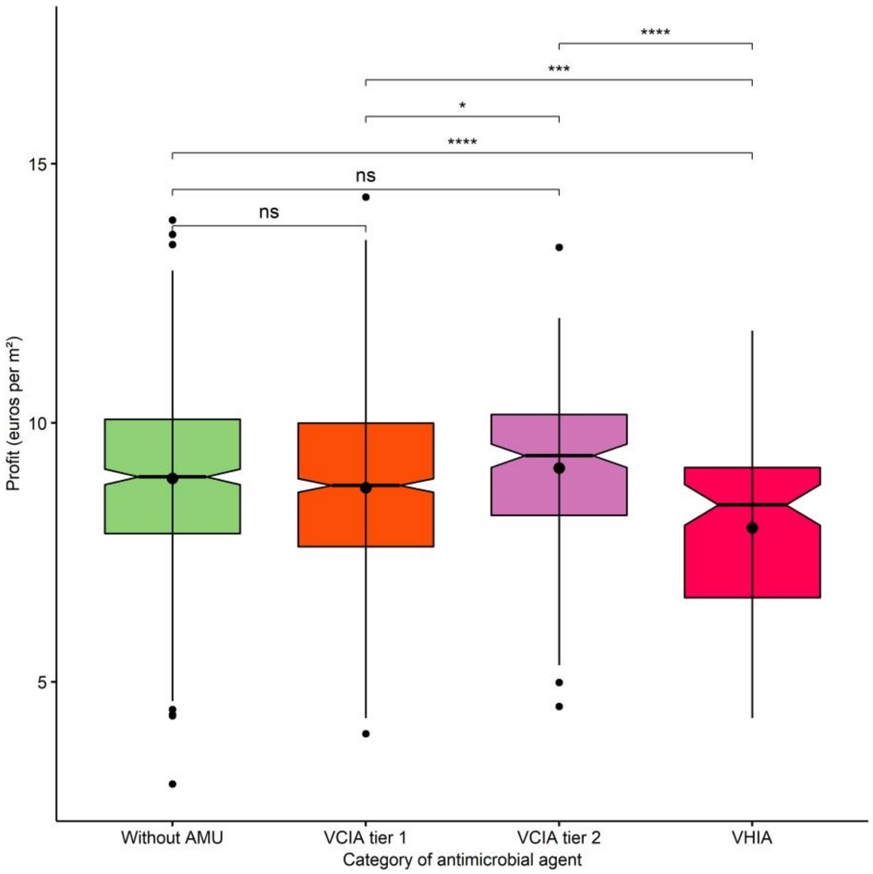

Figure 5. Relationship between economic performance and antimicrobial class, displaying the characteristics of flocks according to ranking criteria for the WOAH. VCIA in our dataset: Tier 1: amoxicillin, ampicillin, phenoxymethylpenicillin, spectinomycin, sulfadiazine, trimethoprim and tylosin; Tier 2: enrofloxacin. VHIA in our dataset: colistin, flumequin and lincomycin.

only to a temporary increase of AMU for therapeutic purposes.[34] In the case of strict intensity standards, they may even have the negative side effect of decreasing animal welfare in a setting where antimicrobials are necessary and there are no substitutes available but that the quota of use has already been reached. European veterinarians responding to a survey conducted[35] noticed that banning metaphylaxis without adapting herd management would unavoidably lead to increased mortality and morbidity.

Policymakers can also adopt voluntary instruments such as economic incentives, agreements and industry self-regulation actions.[29] These instruments are based on an approach intended to promote virtuous behaviour. These measures, which are often used in environmental policies, are increasingly used in public health policies.[36] More specifically, economic instruments such as taxes or subsidies fill the gaps in market mechanisms via an adjustment to internalize externalities. In practice, however, it should be noted that these economic instruments are often used to supplement regulatory measures and not to replace them.

Policies encouraging farmers to work upstream to prevent disease occurrence have the potential to be more useful. Encouraging adequate biosecurity and infection control practices

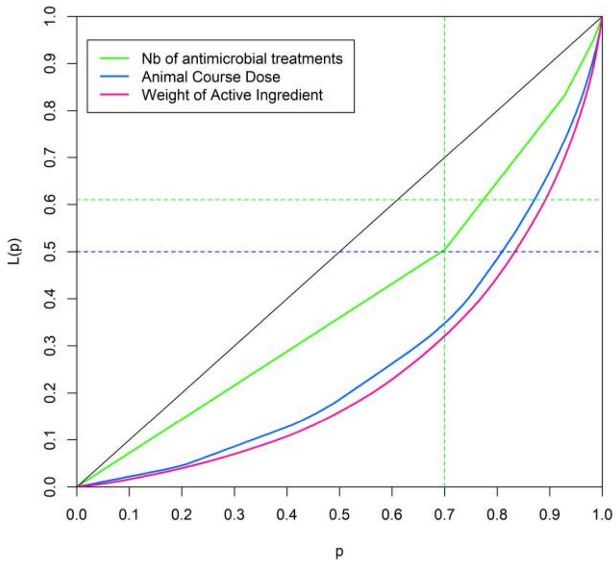

Figure 6. Lorentz curves. The *y*-axis refers to the density function of antimicrobial prescription regarding to antimicrobial indicators (number of antimicrobial treatments, ACD, WAI), while the *x*-axis shows the proportion of flocks.

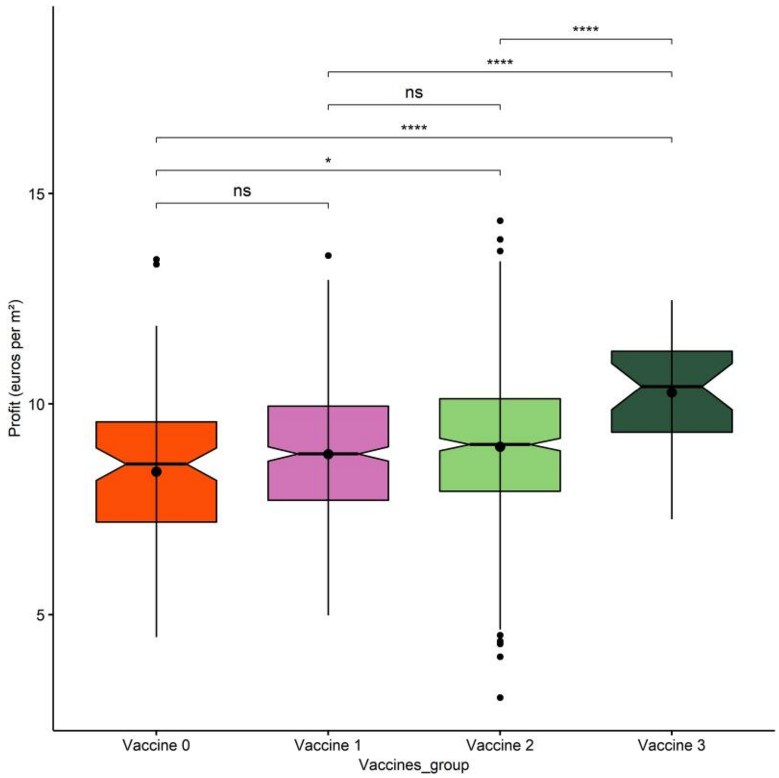

Figure 7. Relationship between the number of vaccine treatments and economic performance. 'Vaccine 0' corresponds to flocks that received 0 doses of vaccines. In addition, 'Vaccine 1', 'Vaccine 2' and 'Vaccine 3' represent flocks that received 1, 2 and 3 vaccine doses, respectively.

Table 1. Profit per m^2 estimations using IV method

	Dependent variable			
	Profit per m^2			
	Linear regression without farmer effects (1)	Linear regression with farmer effects (2)	Quadratic regression without farmer effects (3)	Quadratic regression with farmer effects (4)
Average_age (days)	0.1571***	0.1680***	0.1538***	0.1645***
	(0.0381)	(0.0373)	(0.0512)	(0.0517)
ADG (g/day)	0.1178***	0.1143***	0.1160***	0.1109***
	(0.0137)	(0.0134)	(0.0184)	(0.0187)
Density	0.4779***	0.4293***	0.6171***	0.5665***
	(0.0686)	(0.0678)	(0.1018)	(0.1027)
nb_treatments	−2.0287***	−1.9696***	4.1260***	4.2063***
	(0.3410)	(0.3311)	(0.9427)	(0.9559)
I(nb_treatments)^2			−2.2914***	−2.3331***
			(0.4872)	(0.4941)
Nb_vaccines	0.4233***	0.4207***	0.2755**	0.2807**
	(0.1020)	(0.0996)	(0.1293)	(0.1306)
ID_Farmer		0.00001***		0.00001***
		(0.000002)		(0.000003)
Constant	−12.6619***	−12.0909***	−16.8374**	−16.1544***
	(2.1449)	(2.1056)	(2.9290)	(2.9583)
Observations	1086	1086	1086	1086

Standard errors in brackets. *$P<0.1$; **$P<0.05$; ***$P<0.01$.

by subsidizing them would benefit farmers and society. This encouragement could take the form of improving farm infrastructure and adopting stewardship programmes. Once such beneficial practices have been adopted, it is likely that farmers will maintain them, even in the absence of public incentives. As rational decision-makers, farmers will adopt practices only if their marginal benefit exceeds their marginal costs.[37] If the marginal cost of using fewer antimicrobials is higher, then public incentives would be required to accelerate their adoption. If the marginal cost is lower than the expected benefits, nudging practices would be sufficient.[38,39]

As with any model-based study, our analysis is subject to limitations. The scope of the econometric results was limited for two reasons. On the one hand, our study focused on conventional broiler production. Given the high homogeneity of the production system, our work can be generalized, as we carried out the analysis on an area of France where more than 80% of production occurs in the broiler sector. However, the non-linear relationship between AMU and the economic performance of farms may not be observed in other food animal production sectors. On the other hand, there are no comparative studies in other countries to assess the impact of the Kuznets-style development of AMU on economic performance. Therefore, one avenue for future research would be to assess this inverted-U relationship on a macroeconomic scale. Beyond the scope of our study, the rationale behind farmers' decision-making regarding AMU must be studied. Assessing individual decision-making processes would help in understanding farmers' and veterinarians' behaviours in disease management and in developing innovative and tailored responses to help solving the AMR challenge.

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Transparency declarations

None to declare.

Supplementary data

Supplementary material, including Figures S1 to S5 and Tables S1 to S3, is available as Supplementary data at *JAC-AMR* Online.

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