

## Quantitative and qualitative analysis of antimicrobial usage at farm and flock level on 181 broiler farms in nine European countries

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**Objectives:** To control the emerging threat of antimicrobial resistance, international policy appeals for appropriate monitoring of antimicrobial usage (AMU) at supranational, species and farm level. The aim of this study was to quantify AMU in broilers at farm and flock level in nine European countries.

**Methods:** Antimicrobial treatment data of one flock and purchased antimicrobials over one year were collected at 181 European broiler farms. Afterwards AMU was quantified using treatment incidence (TI) per 100 days based on Defined Daily Dose (DDDvet), Defined Course Dose (DCDvet) or Used Daily Dose (UDDvet) values. Total AMU at flock level was obtained by summing the  $TI_{DDvet}$  of all treatments in the sampled flock ( $TI_{DDvetFl}^*$ ).

**Results:** The median  $TI_{DDvetFl}^*$  was 9.0 (95% CI 5.5–10.8), meaning that broilers were treated with antimicrobials during 9% of their rearing period.  $TI_{DDvetFl}^*$  varied considerably within and between countries. However, in every country at least one untreated flock was present. Average  $TI_{DDvetFl}^*$  at country level ranged from 3.3 to 36.7. Polymyxins, extended-spectrum aminopenicillins and fluoroquinolones were the most used antimicrobials, accounting for 26%, 26% and 18% of total AMU, respectively. Twenty-six percent of the farms started a treatment on day 1 of production, and 49% of overall AMU was administered within the first week.

**Conclusions:** Results show that rearing broilers without AMU is feasible. However, a huge variation in AMU in terms of amount, moment of administration and antimicrobial classes was observed. This shows that there is still ground to be covered when it comes to AMU on broiler farms.

### Introduction

Antimicrobials have shaped modern medicine. Major surgeries have become routine procedures thanks to the prophylactic use of antimicrobials. However, due to the exposure of bacteria to antimicrobials, many intrinsically susceptible bacteria have acquired antimicrobial resistance (AMR) mechanisms, which result in a selective advantage when the bacteria are exposed to antibiotics. This led to the recognition by the WHO of AMR as one of the major threats to public and animal health.<sup>1</sup>

The strongest driver for the selection of AMR is antimicrobial usage (AMU), both in human and veterinary medicine.<sup>2–4</sup> Broiler production is likely to be responsible for a large share of animal-related AMU. It is not only the second biggest European meat-producing industry, but also a very intensive animal production system.<sup>5</sup> Antimicrobials used at flock level are administered via

drinking water, which is the only feasible administration route. However, this type of mass medication leads to frequent exposure to antimicrobials of large numbers of animals and often results in improper dosing of the administered antimicrobials.<sup>6,7</sup>

Phasing out antimicrobial growth promoters in 1999, and the complete ban in 2006, were the first important measures towards constraining AMU in animals in Europe.<sup>8</sup> Following these regulations, several studies observed an increase in therapeutic AMU.<sup>9–11</sup> In 2005, the WHO published the first list of critically important antimicrobials (CIAs), updated to the fifth revision in 2017, with the aim of reducing the use of CIAs in food animal production.<sup>12–14</sup> In 2009, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) was founded, which succeeded in the harmonized collection of European antimicrobial sales data. The results have repeatedly demonstrated huge differences between

countries in the amounts of antimicrobials sold.<sup>15</sup> However, because data are not collected by species, differences in dosage cannot be accounted for, nor does the used indicator allow monitoring of AMU at farm or flock level. Moreover, the indicator's denominator includes all biomass produced per country, which is highly influenced by the composition of the national animal population. Therefore, reports on AMU based on sales figures by country remain a crude measurement with necessary approximations,<sup>16</sup> and conclusions on usage profiles based upon the ESVAC data are debatable.<sup>17</sup> Avoiding approximations is only possible when collecting the actual use of antimicrobials at the farm itself.<sup>18</sup> However, multi-country studies collecting AMU data in broilers at farm level are laborious and time-consuming and to our knowledge inexistent.

To optimize the control of AMU in Europe, appropriate and detailed supranational monitoring of antimicrobials administered at animal species and farm level is required.<sup>2,18,19</sup> Therefore, the aim of this study was to quantify AMU in broilers at farm and flock level in nine European countries in a standardized manner to gain better insights into AMU in broilers. All data was collected within the EU-FP7 'Ecology from Farm to Fork Of microbial drug Resistance and Transmission' (EFFORT) project, which investigates the epidemiology and ecology of AMR in food-producing animals, the environment and humans to quantify AMR exposure pathways for humans.

## Materials and methods

### Study sample and data collection

In a cross-sectional survey, AMU data was collected at 20 farms (21 in country A) in each of the nine participating countries: Belgium, Bulgaria, Denmark, France, Germany, Italy, Poland, Spain and the Netherlands. The selection of farms in each country was based on inclusion criteria to obtain a group of farms that were comparable between and within countries. All farms were conventional and had all-in all-out production with a maximum slaughter age of 50 days. No slow-growing breeds or stocking density lower than 10 birds/m<sup>2</sup> were allowed. In each country, farms were selected based on these criteria in an agreement with local farming organizations, and partially also based on convenience (e.g. distances to farms); regional stratification was used whenever possible. As a result, the 20 farms cannot be considered representative for broiler production in a country. Countries were anonymized (letters A to I). A detailed description can be found in Appendix A (Appendices available as [Supplementary data](#) at JAC Online).<sup>20</sup>

Participating farms were visited between May 2014 and June 2016. A questionnaire was completed in collaboration with the farmers to provide information on farm technical and AMU data. A strict questionnaire protocol in combination with training for the researchers was used to minimize interview bias (Appendix B). Information was listed for each antimicrobial treatment given to the sampled flock. These data are referred to as the treatment data (shown with a superscripted single asterisk). Furthermore, data on purchased antimicrobials during the year preceding the visit was collected. When available information did not cover a whole year, data were extrapolated. These data are referred to as the purchase data (shown with a superscripted double asterisk).

### AMU quantification

AMU was quantified in a standardized manner using treatment incidence (TI) as described by Persoons *et al.*<sup>7</sup> The numerator (Table 1) equals the total amount of active substance (AS) administered (treatment data) or purchased (purchase data). In the denominator, three different parameters

can be used, resulting in three different formulas (Table 1): Defined Daily Dose (DDDvet), Defined Course Dose (DCDvet) or Used Daily Dose (UDDvet). Hereby, TI is expressed as the number of DDDvet or UDDvet administered per 100 animal-days at risk or the number of days per 100 animal-days that the flock is receiving a dose of antimicrobials, reflecting the percentage of time that a broiler is treated with antimicrobials in its life. When using DCDvet,  $TI_{DCDvet}$  expresses the number of treatment courses per 100 animal-days. When using UDDvet, the formula to calculate  $TI_{UDDvet}$  can be simplified (Table 1), as UDDvet, which expresses the administered dose of AS per day per kg of broiler, appears both in the numerator and in the denominator of the formula.

DDDvet and DCDvet reflect the assumed average dose of a drug for its main indication per day per kg of broiler and per treatment course per kg of broiler, respectively. For antimicrobials registered for broilers, most of these values have been defined by ESVAC.<sup>21</sup> Whenever combination products were not on the ESVAC list and the dose of one or both ASs were substantially different from the single AS products, DDDvet and DCDvet values were obtained from the summary of product characteristics (SPC). In all other cases of combination products, the assigned DDDvet/DCDvet values were the same as for the single AS antimicrobials.<sup>21</sup>

When using antimicrobial treatment data, 'kg of animal at risk' was calculated by multiplying 'standard weight' and 'number of animals at the start of the sampled flock'. For purchase data, 'kg of animal at risk' was determined by multiplying 'standard weight' and 'number of animals delivered to slaughter yearly'. 'Standard weight' was set to be 1 kg in accordance with the ESVAC guidelines.<sup>22</sup> For both treatment and purchase data, 'number of days at risk' for each country was set to be equal to the average duration of the rearing period within that country (Table S1).

The different types of TI were calculated based on the treatment data ( $TI_{DDDvet}^*$ ,  $TI_{DCDvet}^*$ , and  $TI_{UDDvet}^*$ ) and a second time based on the purchase data ( $TI_{DDDvet}^{**}$ ,  $TI_{DCDvet}^{**}$ ). For the treatment data, UDD was sometimes expressed per 'kg of feed' or 'litre of water' instead of per 'kg of animal'. Therefore, assumptions were made concerning standard daily feed and water intake for a bird of 1 kg, which were set at 120 g and 210 mL, respectively.  $TI_{DDDvet}$ ,  $TI_{DCDvet}$ , and  $TI_{UDDvet}$  were calculated at flock level by adding up the TIs of all treatments, resulting in  $TI_{DDDvetFI}^*$ ,  $TI_{DCDvetFI}^*$  and  $TI_{UDDvetFI}^*$  respectively.  $TI_{DDDvet}$  and  $TI_{DCDvet}$  were also calculated at farm level by adding up the TIs of all the purchased products, resulting in  $TI_{DDDvetFa}^{**}$  and  $TI_{DCDvetFa}^{**}$ .

### Data processing

Data were entered into EpiData version 3.1 software (EpiData Association, Denmark) by the researchers who visited the farms. Data quality checks were performed using ActivePerl 5.24.1 (ActiveState Software Inc.) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Subsequently, SAS was used for database management. Finally, 10% of all questionnaires were entered twice and compared in SAS to check for data entry quality. All inconsistencies were corrected and datasets from countries with a high percentage of inconsistencies (>5%) were thoroughly re-evaluated by the respective institutes. Next, data required for AMU quantification were imported into Microsoft Excel and a second, more in-depth, quality control was performed prior to the AMU quantification.

### Statistical analysis

Descriptive statistics were calculated in Excel<sup>®</sup> 2016. Since TIs at country level deviated considerably from normality, even after log<sub>10</sub> transformation, minimum, median and maximum results are reported. Median values are reported with 95% CI based on the adjusted bootstrap percentile method with 1000 replicates.<sup>23</sup> To compare different systems of data collection and quantification, results of all TIs were compared with Spearman's rank correlation tests in R version 3.4.0 software (<https://cran.r-project.org>). Only for the indicators based on purchase data, results from country I were not included, as the sampled period only covered one

**Table 1.** Formulas to quantify AMU using TI

| Variable             | Formula   | Result                                 |
|----------------------|---|--|
| Numerator*           | $\text{UDDvet (mg/kg/day)} \times \text{treatment duration (days)} \times \text{no. of animals treated} \times \text{standard weight per animal (kg)}$                              | total amount of AS administered        |
| Numerator**          | $\text{package size} \times \text{no. of packages purchased} \times \text{concentration of AS in the product}$  | total amount of AS purchased           |
| TI <sub>DDvet</sub>  | $\frac{\text{total amount of AS administered* or purchased** (mg)}}{\text{DDvet (mg/kg/day)} \times \text{no. of days at risk} \times \text{kg of AAR}} \times 100 \text{ AAR}$     | no. of DDvet/100 broilers at risk/day  |
| TI <sub>DCDvet</sub> | $\frac{\text{total amount of AS administered* or purchased** (mg)}}{\text{DCDvet (mg/kg/course)} \times \text{no. of days at risk} \times \text{kg of AAR}} \times 100 \text{ AAR}$ | no. of DCDvet/100 broilers at risk     |
| TI <sub>UDDvet</sub> | $\frac{\text{treatment duration} \times \text{no. of animals treated}}{\text{no. of days at risk} \times \text{no. of AAR}} \times 100 \text{ AAR}$                                 | no. of UDDvet/100 broilers at risk/day |

TI<sub>DDvet/DCDvet/UDDvet</sub>, TI calculated with DDvet/DCDvet/UDDvet as a parameter to take dosage into account; AAR, animals at risk.

\*Numerator is based on the treatment data.

\*\*Numerator is based on the purchased data.

month, making extrapolation to a period of 1 year unreliable. Seventy per cent of the remaining farms reported data that covered at least 9 months.

## Results

### AMU at flock level

Based on the treatment data, the median TI<sub>DDvetFl</sub>\* over all flocks was 9.0, with a large variation, ranging from 0 to 174.5. This variation was observed within each group of flocks in each country, with both untreated and treated flocks in every country. In total, 230 treatments, which were all group treatments, were registered over 114 flocks, meaning that 67 flocks (37%) did not receive antimicrobials. Countries C, F and I had a higher percentage of untreated flocks, with 85%, 75% and 85%, respectively, compared with only 5% in countries D and G. Nonetheless, the highest TI<sub>DDvetFl</sub>\* in country C (46.3) was almost equal to the one from country H (46.1), although there were four times more untreated flocks in country C ( $n = 17$ ). The variation in AMU between flocks within the same country and between flocks of different countries is presented in Figure 1 and Table 2.

When comparing different indicators, results correlate only moderately when comparing estimates based on purchase data with estimates based on treatment data of one rearing period, with a correlation coefficient of 0.54 for TI<sub>DDvetFl</sub>\* and TI<sub>DDvetFa</sub>\*. However, they correlate strongly when comparing different quantification methods within the same dataset, ranging from 0.91 to 0.99 (Table 3). Further description of the results is based on the treatment data, as this allows for a more detailed description, and will solely be based on TI<sub>DDvetFl</sub>\* because of the high correlations within the treatment dataset.

### AMU divided over the different antimicrobial classes

Polymyxins, which were represented only by colistin (28 treatments), and extended-spectrum penicillins (ES penicillins), which were represented by amoxicillin (60 treatments) and ampicillin (4 treatments), were the most frequently used antimicrobial classes. Each class represented 26% of total AMU. Polymyxins was the most administered antimicrobial class in country H (43%) and country D (50%) and was used in five out of nine countries. ES penicillins and fluoroquinolones (17% of total AMU) were used in all countries, except in country C, where 72% of total AMU consisted

of tetracyclines. In countries A, D and I, ES penicillins was the most commonly used class of antimicrobials, representing 31%, 30% and 45% of the each country's total AMU, respectively. In country G, fluoroquinolones was the most frequently used antimicrobial class, representing 31% of total usage within that country. Table 4 shows an overview, including ATCvet codes.<sup>24</sup>

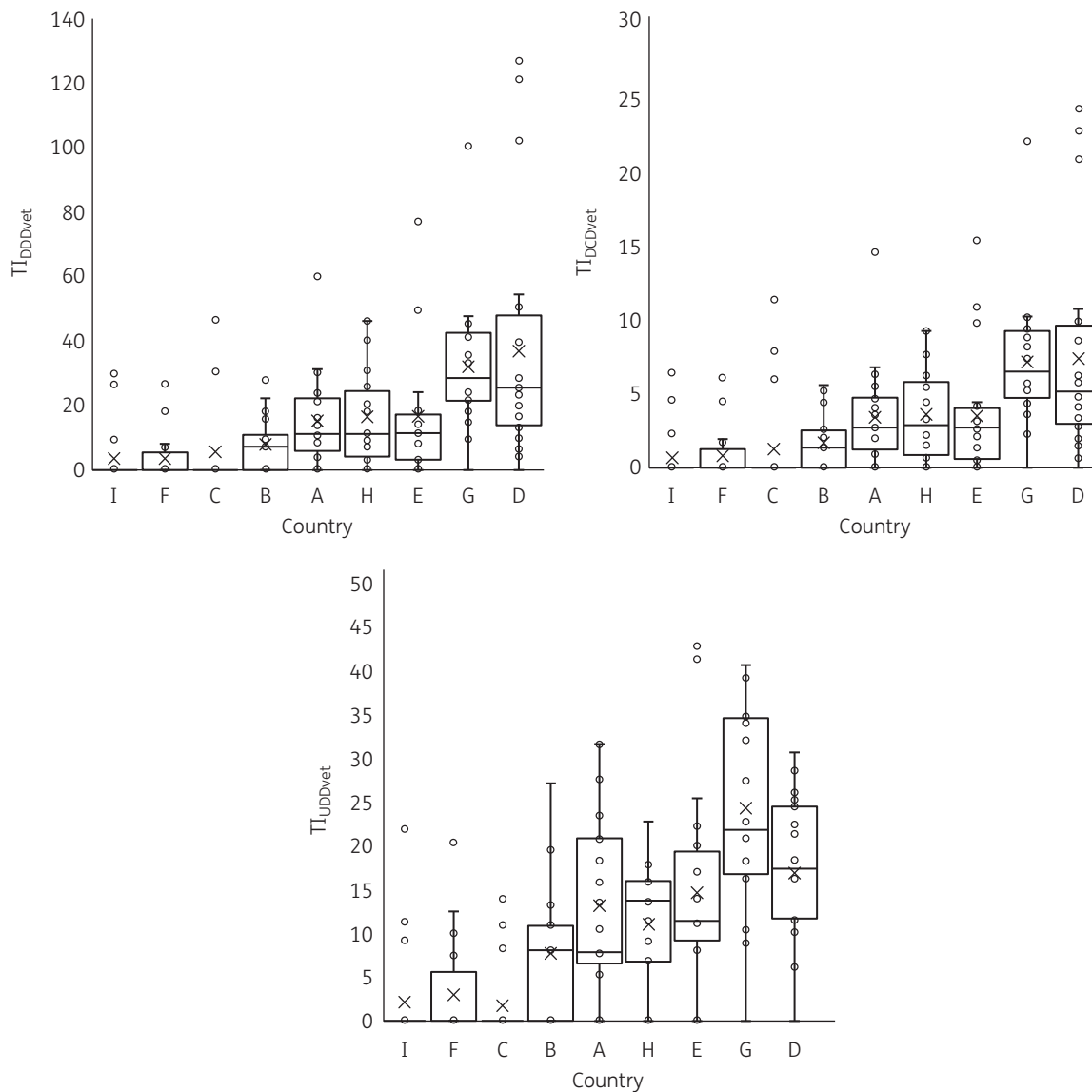
### Indication for treatment

Intestinal disorders were the most common indication for treatment (45%), followed by colibacillosis (16%) and omphalitis (12%) (Table 5). Other indications only represented incidental treatments. Variation between countries was rather limited, except for a few outliers within certain indications such as reported respiratory disorders in country A ( $n = 9$ ) and country G ( $n = 10$ ).

### AMU usage over the period of one production cycle

In 26% of the flocks, antimicrobial treatments were initiated on the first day of production, followed by 9% and 5% on days 2 and 3, respectively (Figure 2). As a result, 38% of the flocks were being treated with antimicrobials on day 3. Subsequently, the percentage of farms where antimicrobials were being administered gradually declined to 2% on day 13, followed by a slight increase resulting in a fluctuation around 10% during the third and fourth week. No new treatments were initiated from day 37 onwards, except for one on day 38 and one on day 42. The early AMU peak was present in all countries, ranging from 10% of the flocks being treated in country C to 65% in country E (Table S2). In the treated flocks from country C ( $n = 3$ ), all treatments were administered within the first three days of production.

Indication for treatment also varied depending on the age of the broilers. On day 1 the 'non-specific' indication was the most frequently used reason to start treatment, accounting for 23% of treatments started on day 1. Over the whole first week, omphalitis was the most frequently reported indication for treatment (27%). Intestinal disorders were most frequently reported between the third and fifth weeks (67%) (Table S3). Furthermore, the type of antimicrobial used varied widely throughout the rearing period. While lincomycin/spectinomycin was only used in treatments initiated on day 1 ( $n = 16$ ) and day 2 ( $n = 3$ ), ES penicillin treatments ( $n = 64$ ) were registered on 29 different days during the six weeks of production. Fluoroquinolones ( $n = 50$ ) were mainly used at the



**Figure 1.** Comparison of antimicrobial TI at flock level ( $TI_{f1}$ ) across nine European countries (A–I). TI is shown as the number of DDDvet ( $TI_{DDvet}$ , top left corner), DCDvet ( $TI_{DCDvet}$ , top right corner) and UDDvet ( $TI_{UDDvet}$ , bottom centre) per 100 broiler-days at risk. TI represents the percentage of time that a broiler was treated with antimicrobials in its life. Antimicrobial treatment data were obtained from 181 broiler farms with 20 farms in each country (A–I, 21 in country A). On each farm, data were collected from one flock from day 1 to slaughter. The full black line within each box plot represents the median. The black cross within each box plot represents the average. The whiskers extend to the most extreme data point within the range of  $1.5 \times IQR$  from the box. Outliers, data points outside the range of the whiskers, are shown as open circles.

beginning of production ( $n = 30$ ). A similar pattern was seen for the aminoglycosides, with seven out of the nine treatments being applied on day 1 (Table S4).

## Discussion

Previous studies have described AMU in multiple species;<sup>9,11,25</sup> others only studied one species.<sup>7,26–28</sup> In most cases they only covered one country or did not use the same methodology across countries.<sup>17</sup> When multi-country studies on AMU implemented the same methodology, results were mainly based on sales data, prohibiting detailed description of AMU at farm or

flock level or direct species comparison.<sup>8,11,15</sup> To our knowledge this is the first multi-country study that reports on AMU in broilers in such detail, using standardized sampling and AMU quantification protocols.

There is no consensus on which indicator provides the most valuable information when quantifying AMU, as characteristics such as resolution, ability to assess exposure and comparability differ between indicators.<sup>16</sup> To describe and compare AMU for broilers at flock level, it is required to use an indicator with a high spatial resolution (on-farm registration) and high comparability between flocks.  $TI_{DDvet}$  fulfils almost all requirements described by Collineau *et al.*,<sup>16</sup> as quantification is based on treatments

**Table 2.** Overview of the quantification of AMU, expressed in TI at the flock level ( $TI_{DDvetFl}^*$ ,  $TI_{DCvetFl}^*$  and  $TI_{DDvetFl}^*$ ) and the farm level ( $TI_{DDvetFa}^{**}$ ,  $TI_{DCvetFa}^{**}$ )

| Country              | NUF* | Median (95% CI) [minimum–maximum] |                             |                             |                               |                            |
|----------------------|------|-----------------------------------|-----------------------------|-----------------------------|-------------------------------|----------------------------|
|                      |      | $TI_{DDvetFl}^*$                  | $TI_{DCvetFl}^*$            | $TI_{DDvetFl}^*$            | $TI_{DDvetFa}^{**}$           | $TI_{DCvetFa}^{**}$        |
| A                    | 2    | 11.1 (5.5–16.0) [0.0–59.7]        | 2.7 (1.3–4.0) [0.0–14.6]    | 7.9 (5.3–7.9) [0.0–31.6]    | 12.5 (8.7–15.4) [1.9–22.8]    | 2.7 (1.9–3.4) [0.4–5.1]    |
| B                    | 7    | 7.0 (0.0–6.9) [0.0–27.7]          | 1.4 (0.0–1.4) [0.0–5.5]     | 8.1 (0.0–8.1) [0.0–27.0]    | 15.5 (7.3–34.6) [1.1–159.8]   | 3.2 (1.4–6.4) [0.2–30.3]   |
| C                    | 17   | 0.0 <sup>a</sup> [0.0–46.3]       | 0.0 <sup>a</sup> [0.0–11.4] | 0.0 <sup>a</sup> [0.0–13.9] | 0.0 <sup>a</sup> [0.0–11.1]   | 0.0 <sup>a</sup> [0.0–2.7] |
| D                    | 1    | 25.4 (16.3–34.1) [0.0–174.5]      | 5.2 (3.3–6.9) [0.0–24.3]    | 17.4 (12.2–22.5) [0.0–30.6] | 50.3 (28.6–82.3) [12.2–166.2] | 9.8 (5.9–16.0) [2.5–33.4]  |
| E                    | 3    | 11.2 (3.2–13.4) [0.0–76.9]        | 2.7 (0.9–3.1) [0.0–15.4]    | 11.3 (11.2–15.5) [0.0–42.9] | 1.5 (0.9–2.7) [0.0–147.9]     | 0.3 (0.2–0.5) [0.0–28.5]   |
| F                    | 15   | 0.0 <sup>a</sup> [0.0–26.5]       | 0.0 <sup>a</sup> [0.0–6.1]  | 0.0 <sup>a</sup> [0.0–20.4] | 4.0 (2.6–5.3) [0.5–44.5]      | 0.9 (0.6–1.2) [0.1–10.1]   |
| G                    | 1    | 28.4 (21.2–37.6) [0.0–101.0]      | 6.5 (4.7–8.7) [0.0–22.1]    | 21.8 (18.4–33.3) [0.0–40.7] | 17.8 (9.6–37.5) [2.9–209.1]   | 3.9 (2.1–8.3) [0.7–45.6]   |
| H                    | 4    | 11.0 (6.8–20.4) [0.0–46.1]        | 2.8 (1.5–4.9) [0.0–9.2]     | 13.6 (6.8–14.8) [0.0–22.7]  | 10.8 (2.0–15.7) [0.0–61.5]    | 2.4 (0.7–3.9) [0.0–13.3]   |
| I                    | 17   | 0.0 <sup>a</sup> [0.0–29.7]       | 0.0 <sup>a</sup> [0.0–6.4]  | 0.0 <sup>a</sup> [0.0–22.0] | 8.5 (2.1–16.3) [0.0–771.2]    | 2.1 (0.8–4.9) [0.0–97.7]   |
| All, median (95% CI) | 67   | 9.0 (5.5–10.8)                    | 2.0 (1.3–2.6)               | 8.5 (7.8–10.9)              | 9.2 (5.7–11.5)                | 2.0 (1.2–2.5)              |

At flock level, data are based on antimicrobial treatments administered to a flock of broilers from day 1 to slaughter, with a total of 181 participating flocks in nine countries (20 flocks/country, 21 flocks in country A). At farm level, data are based on antimicrobials purchased on a broiler farm during 1 year, with a total of 181 participating farms in nine countries (20 farms/country, 21 farms in country A).  $TI_{DDvetFl}^{*/**}$  and  $TI_{DCvetFl}^{*/**}$  express the number of days per 100 animal-days that the flock received a dose of antimicrobials.  $TI_{DDvetFl}^{*/**}$  expresses the number of treatment courses that the flock received per 100 animal-days. NUF\*, number of untreated flocks in treatment dataset. 95% CI is based on the adjusted bootstrap percentile method with 1000 replicates.

<sup>a</sup>Because of the high frequency of zero use, no 95% CI for the median could be estimated with the adjusted bootstrap percentile method.

\*Based on the treatment data.

\*\*Based on the purchase data.

**Table 3.** Correlations and their P values (Spearman's rank correlation) between the different indicators for quantifying AMU

| Variable            | $TI_{DDvetFl}^*$     | $TI_{DCvetFl}^*$     | $TI_{DDvetFl}^*$     | $TI_{DDvetFa}^{**}$  | $TI_{DCvetFa}^{**}$ |
|---------------------|----------------------|----------------------|----------------------|----------------------|---------------------|
| $TI_{DDvetFl}^*$    | 1                    |                      |                      |                      |                     |
| $TI_{DCvetFl}^*$    | 0.99 ( $P < 0.001$ ) | 1                    |                      |                      |                     |
| $TI_{DDvetFl}^*$    | 0.93 ( $P < 0.001$ ) | 0.92 ( $P < 0.001$ ) | 1                    |                      |                     |
| $TI_{DDvetFa}^{**}$ | 0.54 ( $P < 0.001$ ) | 0.54 ( $P < 0.001$ ) | 0.49 ( $P < 0.001$ ) | 1                    |                     |
| $TI_{DCvetFa}^{**}$ | 0.55 ( $P < 0.001$ ) | 0.54 ( $P < 0.001$ ) | 0.49 ( $P < 0.001$ ) | 0.99 ( $P < 0.001$ ) | 1                   |

AMU was quantified using TI. On one hand, TI is expressed at flock level by  $TI_{DDvetFl}^*$ ,  $TI_{DCvetFl}^*$  and  $TI_{DDvetFl}^*$ , which are based on the antimicrobial treatments given to a flock from day 1 to slaughter. On the other hand, TI is expressed at farm level by  $TI_{DDvetFa}^{**}$  and  $TI_{DCvetFa}^{**}$ , which are based on the antimicrobials purchased on a farm over 1 year. The different TIs were calculated for all 181 participating farms and their sampled flocks.

\*Based on the treatment data.

\*\*Based on the purchased data.

**Table 4.** Proportion (%) by antimicrobial class of the amount of antimicrobials used on 181 participating broiler flocks in nine European countries (20 flocks/country, 21 flocks in country A)

| Antimicrobial class <sup>a</sup> | ATCvet code | Country |       |       |       |       |       |       |       |       | total (%) |
|----------------------------------|-------------|---------|-------|-------|-------|-------|-------|-------|-------|-------|-----------|
|                                  |             | A (%)   | B (%) | C (%) | D (%) | E (%) | F (%) | G (%) | H (%) | I (%) |           |
| Aminoglycosides                  | QJ01GB      | —       | —     | —     | —     | —     | —     | 5     | 6     | —     | 2         |
| ES penicillins                   | QJ01CA      | 31      | 23    | —     | 30    | 24    | 21    | 27    | 18    | 45    | 26        |
| Amphenicols                      | QJ01BA      | —       | —     | —     | —     | —     | —     | 2     | —     | —     | <1        |
| Fluoroquinolones                 | QJ01MA      | 15      | 7     | —     | 6     | 36    | 12    | 31    | 19    | 31    | 18        |
| Linco/spec                       | QJ01FF52    | 14      | 28    | 28    | —     | —     | —     | 1     | —     | —     | 5         |
| Lincosamides                     | QJ01FF      | —       | —     | —     | —     | —     | —     | —     | —     | 23    | 1         |
| Macrolides                       | QJ01FA      | <1      | —     | —     | 6     | —     | —     | 1     | 7     | —     | 3         |
| Other quinolones                 | QJ01MB      | 3       | —     | —     | —     | —     | —     | —     | —     | —     | <1        |
| β-lact-sens penicillins          | QJ01CE      | —       | —     | —     | —     | —     | —     | 3     | —     | —     | 1         |
| Polymyxins                       | QJ01XB      | —       | 20    | —     | 50    | 30    | —     | 14    | 43    | —     | 26        |
| Tetracyclines                    | QJ01AA      | 16      | 21    | 72    | —     | —     | 19    | 15    | 7     | —     | 11        |
| Trim/sulfa                       | QJ01EW      | 21      | —     | —     | 9     | 10    | 48    | 2     | —     | —     | 8         |

Proportions are shown at country level (columns A to I) and in total (total column). All 230 antimicrobial treatments from day 1 to slaughter on the 181 flocks were quantified using TI based on DDD (DDDvet, TI<sub>DDDvet</sub>\*). Linco/spec, lincosamides/spectinomycin; Trim/sulfa, trimethoprim/sulphonamides; β-lact-sens penicillins, β-lactamase-sensitive penicillins.

<sup>a</sup>Antimicrobial classes that are not in this table were not used.

**Table 5.** Distribution (%) by indication for treatment of the total number of treatments within a country (columns A to I) and in total

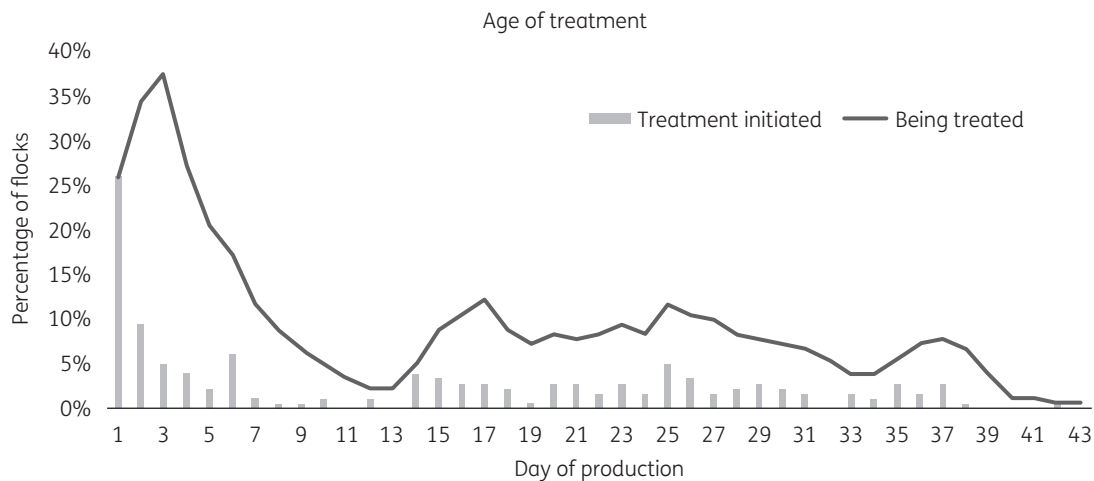
| Indication for treatment | Country                |                        |                       |                        |                        |                       |                        |                        |                       | total (%) |
|--------------------------|------------------------|------------------------|-----------------------|------------------------|------------------------|-----------------------|------------------------|------------------------|-----------------------|-----------|
|                          | A (% <i>, n = 37</i> ) | B (% <i>, n = 15</i> ) | C (% <i>, n = 3</i> ) | D (% <i>, n = 48</i> ) | E (% <i>, n = 29</i> ) | F (% <i>, n = 7</i> ) | G (% <i>, n = 58</i> ) | H (% <i>, n = 28</i> ) | I (% <i>, n = 4</i> ) |           |
| Intestinal disorder      | 35                     | 13                     | 67                    | 90                     | 38                     | 29                    | 36                     | 29                     | 50                    | 45        |
| Colibacillosis           | 3                      | 27                     | —                     | 4                      | 31                     | 43                    | 14                     | 36                     | —                     | 16        |
| Omphalitis               | 22                     | 33                     | —                     | —                      | 10                     | —                     | 19                     | —                      | —                     | 12        |
| Respiratory disorder     | 24                     | 7                      | —                     | 2                      | —                      | —                     | 17                     | 4                      | —                     | 10        |
| Locomotor disorder       | 8                      | 20                     | 33                    | —                      | 3                      | 29                    | 7                      | —                      | —                     | 6         |
| General disorder         | 3                      | —                      | —                     | 4                      | 10                     | —                     | 2                      | —                      | 50                    | 4         |
| Mortality                | 3                      | —                      | —                     | —                      | 7                      | —                     | 2                      | —                      | —                     | 2         |
| Non-specific             | 3                      | —                      | —                     | —                      | —                      | —                     | 3                      | 32                     | —                     | 5         |

Data shown are based on 229 antimicrobial treatments out of 230 treatments that were registered during the rearing period from day 1 to slaughter of 181 broiler flocks in nine European countries (20 flocks/country, 21 flocks in country A). Indication for treatment was missing for one treatment and is therefore not shown in the table.

registered at flock level and takes into account a standardized daily dose (DDDvet) and treatment length. Because of the need to work with a standardized feed and water intake, a standardized animal weight was used instead of the actual animal weight at treatment. Comparability between flocks was achieved by setting up inclusion criteria (Appendix A), resulting in data from comparable broiler production systems across Europe.

The correlation of 0.54 between indicators from different datasets (treatment versus purchase data) is inherent to the type of data collected and can be explained by the different time frames that are covered by the datasets. Hence, an untreated flock does not equal a non-using farm, as other flocks at that farm might be faced with a disease outbreak, possibly leading to higher AMU.

DDDvet values were determined by ESVAC based on the recommended dosage found in the SPC of the drugs in nine European countries.<sup>29</sup> However, ESVAC reports these values as technical units of measurement that should not be considered to reflect the actual daily dose in all circumstances, as they are often a compromise between different approved doses for the same AS in different countries or different commercialized products in the same country.<sup>21,30</sup> In contrast, the UDD can differ between and within farms, as it represents the truly administered dose of a drug on the farm itself. The flexibility of UDD makes the indicator robust to deviation from the SPC and is therefore a better reflection of the true exposure at flock level.<sup>28,31,32</sup> Yet, the limitation of the UDD is the requirement for very detailed herd-level data collection. Nonetheless, from the



**Figure 2.** The histogram shows the proportion (%) of the broiler flocks (on the y-axis) where treatment with antimicrobials was initiated on a certain day of production (on the x-axis). The graph shows the proportion (in percentage) of the 181 broiler flocks (on the y-axis) that were being treated with antimicrobials on a certain day of production (on the x-axis). The x-axis represents the age of the broilers in days as it covers one rearing period from day 1 until day 43. Data shown are based on all 230 antimicrobial treatments that were registered during the rearing period from day 1 to slaughter of 181 broiler flocks in nine European countries.

obtained results it appears that  $TI_{DDvetFl}^*$  and  $TI_{UDvetFl}^*$  seem to correlate strongly (0.93). This does not mean that at flock level the parameters are comparable in all circumstances as the biggest range for these parameters is represented by a flock where  $TI_{DDvetFl}^*$  equalled 121.0, compared with 12.2 for  $TI_{UDvetFl}^*$ . However, on a meta level, the results did correlate quite well. This is important since DDDvet is more convenient to report in a harmonized manner compared with the detailed actual exposure as measured by means of the UDDvet. The TI was also calculated using DCDvet to describe the number of courses rather than the number of treatment days. Again, results for both  $TI_{DDvet}$  and  $TI_{DCDvet}$  appeared to be very strongly correlated (0.99) and provided comparable information. The only difference was the scale, which is on average four and a half times smaller in  $TI_{DCDvet}$ , reflecting the truly observed average treatment duration of 3.5 days. The methodology used to determine DCDvet values<sup>29</sup> and outliers regarding treatment duration may explain the small difference between the average treatment duration (3.5 days) and the average ratio between  $TI_{DDvet}$  and  $TI_{DCDvet}$  (4.5 days).

This study has clearly demonstrated that AMU differs considerably between flocks, both within and between countries. The same finding was previously reported in a study on AMU in pigs in four European countries.<sup>27</sup> In addition, other studies conducted at flock or farm level also reported a large variation.<sup>7,9,26,28</sup> In each country there were farms that succeeded in rearing the sampled flock without antimicrobial treatments and flocks that stood out by higher usage. This shows that there is substantial room for improvement towards more responsible AMU in the majority of the farms.

Three AMU classes represented 70% of all the antimicrobials administered in this study. However, each country had a different distribution of antimicrobial classes used. This variation between countries was also observed for pigs<sup>27</sup> and for AMU in veterinary medicine in general, as reported in ESVAC reports.<sup>33</sup> These variations may be the result of differences in availability of registered antimicrobial products, presence or absence of specific legislation to reduce the use of especially Highest Priority CIAs (HPCIA), or

different levels of clinical resistance.<sup>4,18,27,34</sup> Moreover, other explanations such as economic incentives and experience of the veterinarian have been suggested.<sup>35</sup> By publishing a list of CIAs, the WHO has provided a reference that can be used in risk management by different stakeholders, with the aim to reduce the veterinary use of those antimicrobials pivotal for human healthcare. Nevertheless, fluoroquinolones and polymyxins belonged to the most commonly used classes in this study, despite being on the HPCIA list.<sup>13</sup> However, polymyxins were only added to the list in 2016 while, for the current study, data collection was conducted between 2014 and 2016.

AMU peaked during two moments of the rearing period. The first and highest peak was detected in the first two days of production and represented 27.8% of the total AMU. This peak is likely linked to routinely prophylactic/metaphylactic AMU to prevent diseases such as omphalitis and colibacillosis. This type of mass medication is considered as a cheap and easy solution for disease prevention. Recently, the European Commission published a report with guidelines for prudent use of antimicrobials in veterinary medicine where they call for action regarding the prophylactic and recurrent group medication of poultry, which is often administered before or after transport of day-old chicks to prevent losses in productivity.<sup>36</sup>

During the first peak, omphalitis was the most commonly reported indication, which is probably related to faecal contamination of eggs. This can lead to *Escherichia coli* infections at the moment of hatching, resulting in death or yolk sac infections.<sup>37</sup> The 'non-specific' indication represented 23% of the treatments on the first day of production. Non-specific treatments are problematic as this is in contravention of guidelines on responsible AMU, which indicate the requirement of a proper diagnosis before treatment. A solution to avoid inappropriate AMU in day-old chicks can be found in good management on arrival at the farm.<sup>36</sup> However, within the pyramidal structure of the broiler industry, many factors influence day-old chick quality,<sup>38,39</sup> which emphasizes the importance of good management throughout the entire production chain.

The second treatment peak stretches out over a larger time frame, starting at the beginning of week 3 and slowly disappearing after week 4. In broilers, gastrointestinal problems typically occur during this production period.<sup>40</sup> In the field, these intestinal problems are often referred to as dysbacteriosis. The aetiology of this disorder is not yet fully understood but is most certainly multifactorial,<sup>41</sup> which might explain the high usage of ES penicillins, such as amoxicillin.

In this study we quantified AMU in broiler farms of nine European countries, comparing  $TI_{DDvet}$ ,  $TI_{DCDvet}$  and  $TI_{UDDvet}$ . These different indicators did not show large differences in results when quantification was performed within the same dataset. The type of dataset used (treatment versus purchase), on the other hand, showed substantial differences. When focusing on the treatment data, a huge variation in AMU, in terms of amount administered, moment of treatment and antimicrobial classes, was observed both within and between countries. This calls for further research to determine the drivers causing this variation, so correct actions towards more responsible AMU can be taken.

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## Transparency declarations

None to declare.

## Supplementary data

Tables S1 to S4 and Appendixes A and B are available as [Supplementary data](#) at JAC Online.

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