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French agency for food, environmental and occupational health & safety

Investigate, evaluate, protect

Sales survey of Veterinary Medicinal Products containing Antimicrobials in France - 2014

Annual Report

October 2015 | Scientific Edition

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Authors: French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - French Agency for Veterinary Medicinal Products (ANMV)

Gerard Moulin and Anne Chevance, ANSES-ANMV

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I. Abstract

The French Agency for Veterinary Medicinal Products (ANSES-ANMV) began monitoring sales of veterinary antimicrobials in 1999. Its survey is based on the recommendations of Chapter 6.8 of the OIE Terrestrial Animal Health Code: "Monitoring of the quantities and usage patterns of antimicrobial agents used in food-producing animals".

It is carried out in collaboration with the French Union for the Veterinary Medicinal Product and Reagent Industry (SIMV), based on annual reporting of antimicrobial sales by the pharmaceutical companies marketing them. The companies also provide an estimated breakdown of the drugs sold by target species. The information collected from the laboratories covers 100% of authorised drugs[1].

The information gathered through this national monitoring scheme is one of the essential elements, together with monitoring of bacterial resistance, needed for assessing the risks associated with antimicrobial resistance.

Tonnage of active ingredient sold

In 2014, the total volume of sales of antimicrobials amounted to 781.5 tonnes, an increase of 11.8% compared to 2013, whereas the tonnage of active ingredient had been falling steadily between 2007 and 2013.
Despite this increase in sales of antimicrobials in 2014, the tonnage sold in this year still fell by 23.0% compared to 2010.

The observed increase in sales seems to be related to the publication of Act no. 2014-1170 of 13 October 2014 on the future of agriculture, food and forestry (LAA)[2], which introduced several measures, such as an end to discounts, rebates and reductions on antimicrobials, with effect from 1 January 2015. It seems that, paradoxically, this prospect led the players involved in veterinary medicinal product distribution and/or prescription to accumulate stocks of medicines containing antimicrobials at the end of 2014.
It is usually considered that sales of medicinal products over the year reflect exposure of animals for the same year, on the assumption that all the medicinal products sold were administered to the animals. This premise does not seem valid for 2014, given this stockpiling, which is estimated to cover approximately 3 to 4 months. The change in the turnover of veterinary medicinal products[3] confirms this analysis since, in the first half of 2015, a decrease of around 40% was observed in sales of antimicrobials compared to the first half of 2014. This decline is partly due to the resorption of the stockpile accumulated at the end of 2014.

Exposure to antimicrobials
The ALEA (Animal Level of Exposure to Antimicrobials) is calculated by taking into account differences in potency and dosage between antimicrobials as well as the changes in the animal population. It is based on the assumption that all the antimicrobials sold during a given year were administered to animals in France during this year.

If the ALEA is calculated this year on the basis of the tonnage of antimicrobials sold, an increase of 13.1% can be observed compared to 2013. Assuming that there was stockpiling by the players involved in distributing and/or prescribing veterinary medicinal products, it is not possible to interpret the observed increase in exposure.

[1] The off-label use of veterinary medicinal products is partly taken into consideration in the manufacturers' declarations. Exceptional prescription and off-label use of human drugs or extemporaneous preparations containing antimicrobials under the provisions of the cascade approach (Article L. 5143-4 of the French Code of Public Health) is not taken into account.

[2] http://www.legifrance.gouv.fr/affichLoiPubliee.do;jsessionid=5691BBA0E2987B8FCBB6195E53853F64.tpdjo07v_2?type=general&idDocument=JORFDOLE000028196878

[3] Figures from the French Industry Association for the Study of Veterinary Medicinal Products (AIEMV)

It would therefore be inappropriate this year to conduct a detailed study of ALEAs by species and class of antimicrobials for 2014. The report on next year's sales will calculate exposure by taking into account the sales data for the two years 2014 and 2015, in order to even out any possible stockpiling phenomenon.

- Third- and fourth-generation cephalosporins and fluroquinolones

The ALEA increased for all classes of antimicrobials with the notable exception of third- and fourth-generation cephalosporins and fluoroquinolones.

The ALEA for third- and fourth-generation cephalosporins, all animal species combined, fell by 12% between 2013 and 2014. Between 2013 and 2014, this decrease was 11.7% for cattle, 36.8% for pigs and 3.2% for domestic carnivores.
In the pig sector, there has been a notable decrease of 78.2% since the implementation of the initiative to voluntarily restrict the use of newer-generation cephalosporins.

The ALEA for fluoroquinolones, all animal species combined, fell by 3.5% between 2013 and 2014. Over these last two years, the ALEA increased in poultry (+21.5%), and decreased in cattle (-7.9%), pigs (-3.0%) and domestic carnivores (-1.3%).

The decline in exposure may be even greater if stockpiling by the parties involved in veterinary medicinal product distribution and/or prescription took place for these classes of critical antimicrobials.

Discussion

The phenomenon noted this year strengthens the conclusions of ANSES Opinion No. 2011-SA-0071 on the assessment of the risks of emergence of antimicrobial resistance and the measures of the national plan for the reduction of antimicrobial resistance risks. In this Opinion, published in April 2014, ANSES recommended the introduction of long-term tools for monitoring more closely the administration of antimicrobials on farms, by animal species, by sector and type of production, in order to obtain better quality data each year on the quantities actually administered to animals.

As part of the EcoAntibio 2017 Plan, several initiatives are under way to improve the estimation of exposure to antimicrobials by category of animals, physiological stage or species (for poultry).

The need for more precise data on the use of antimicrobials by species and category of animals is regularly reiterated at European level.

At European level, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) scheme currently allows harmonised collection of antimicrobial sales data without distinguishing between animal species. A reflection paper[4] was published in 2013 to propose a system for collecting data by species and the establishment of "consumption" indicators. In 2014, the European Medicines Agency (EMA) also published a document[5] on the development of DDDAs and DCDAs (dosages and treatment durations that are harmonised at European level). These reference values are expected to be published in late 2015.

At national level, the Act No. 2014-1170 of 13 October 2014 on the future of agriculture, food and forestry provides for the mandatory reporting of sales of antimicrobials by the veterinary pharmaceutical companies, as well as reporting by the parties involved in distribution and/or prescription of veterinary medicinal products. The implementing decrees and orders have not yet been published.

[4] ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136456.pdf

[5] http://www.ema.europa.eu/docs/en_GB/document_library/Overview_of_comments/2015/06/WC500188889.pdf

Conclusion

In France, many measures have been taken since late 2010 to promote the prudent use of antimicrobials:

- initiative in the pig sector on limiting the use of cephalosporins,
- charter on correct use of drug therapies in rabbit farming,
- inter-professional charter on good health management and correct use of drug therapies in veal calf production,
- raising awareness in many sectors about good practice and the rational use of antimicrobials,
- introduction in veterinary medicine of the EcoAntibio 2017 national plan, which is aiming to reduce use of antimicrobials (all classes combined) by 25% in five years, while preserving the therapeutic arsenal,
- ANSES internal request to assess the risk of emergence of antimicrobial resistance associated with patterns of antimicrobial use in the field of animal health, for which the expert report and opinion were published in June 2014,
- Act on the future of agriculture, food and forestry, which has set a target of a 25% reduction in the use of fluoroquinolones and third- and fourth-generation cephalosporins by December 2016, taking 2013 as the reference year,
- change in commercial policies for purchases and sales of antimicrobials (in the framework of the Act on the future of farming),
- etc.

The end to discounts, rebates and reductions established by the Act on the future of agriculture, food and forestry with effect from 1 January 2015 may have led to the accumulation of drugs among the parties involved in the distribution and/or prescription of veterinary medicinal products, which would explain the increase in the quantities sold. In these conditions, the indicators of animal exposure to antimicrobials cannot be interpreted for 2014 because it is inappropriate to take, as in previous years, the basic assumption that every drug sold in the year was administered to an animal. Thus the exposure indicators will not be developed in the framework of this report. On the other hand, next year's report will take into account the quantities sold over two years (2014 and 2015) in order to calculate the average exposure of animals over these two years.

However, while the ALEA has increased for all classes of antimicrobials, it should be noted that this was not the case with third- and fourth-generation cephalosporins and fluoroquinolones. Following a period of stabilisation, the indicator of animal exposure to critical antimicrobials (third- and fourth-generation cephalosporins and fluoroquinolones) has continued to fall over the last few years.

The Act on the future of agriculture, food and forestry sets a new target for reducing the use of cephalosporins and fluoroquinolones by 25% in three years (taking 2013 as the reference year). Reaching this target will require the continuation of measures taken and the introduction of new actions, especially in sectors where the use of these classes of compounds is high.

II. Introduction

Antimicrobial resistance is a public health issue concerning both human and veterinary medicine. Monitoring of sales of antimicrobials is one of the important sources of information used for the assessment and management of risks related to antimicrobial resistance.

The French Agency for Veterinary Medicinal Products (ANSES-ANMV) began monitoring sales of veterinary antimicrobials in 1999. Its survey is based on the recommendations of Chapter 6.8 of the OIE Terrestrial Animal Health Code on "Monitoring of the quantities and usage patterns of antimicrobial agents used in food producing animals".

France also participates in the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) scheme which was launched by the European Medicines Agency (EMA) at the request of the European Commission, with the aim of collecting harmonised data on antimicrobial sales for all countries in the European Union.

In France, monitoring of antimicrobial sales is based on reports by holders of marketing authorisations (MAs) obtained as a result of an agreement with the French Union for the Veterinary Medicinal Product and Reagent Industry (SIMV). All antimicrobials sold in France are recorded through this monitoring.

Antimicrobial sales data are compared with other sources of information such as reported turnover from the companies marketing the veterinary drugs and data from epidemiological surveys of antimicrobial consumption.

The present report describes the veterinary antimicrobial sales for 2014 and includes a comparison with results from previous years.

III. Materials and Methods

a) Data used in this report

Data provided by the Marketing Authorisation (MA) holders

Monitoring of sales is based on a questionnaire sent annually to each Marketing Authorisation (MA) holder who has registered a veterinary medicinal product containing antimicrobials in France. MA holders are asked to declare the number of units sold for each commercial presentation of each veterinary medicinal product. Since 2009, MA holders have also been required to provide information, for each medicinal product, on the breakdown of sales by target species.

These figures are supplied for the period from 1 January to 31 December and therefore cover all veterinary antimicrobials sold in 2014.

Data on the French animal population

To take into account fluctuations in the animal population when interpreting the data, the information published by Agreste[6] is used for food-producing animals.

For domestic pets, data are provided by statistics from FACCO[7] (the French trade federation of food manufacturers for dogs, cats, birds and other pets). These data are published every two years.

Data on dosage and treatment duration

For each drug and each species, the dosage and treatment duration are those defined in the MA.

b) Data validation

To avoid the risk of any reporting errors, sales volumes are compared with annual turnover reported independently by the MA holders. Any discrepancies are investigated. Significant differences compared to previous years are subject to a specific audit.

c) Calculation and interpretation of data

Sales volumes for each commercial presentation are cross-referenced with data available in the ANSES-ANMV veterinary medicinal product database (qualitative and quantitative composition, pharmaceutical form, target species, etc.).

In this report, critical antimicrobials are those belonging to the classes of newer-generation cephalosporins and fluoroquinolones.

Conversion

Calculations are then performed to express the sales in weight of active ingredient. For some active ingredients expressed in international units (IU), as recommended by the European Medicines Agency (EMA) in the framework of the ESVAC scheme, a conversion factor (WHO standard value) is used:

- 74 IU for 1 mg of Bacitracin

[6] http://agreste.agriculture.gouv.fr/
[7] http://www.facco.fr/

- 12700 IU for 1 mg of Colistin methanesulfonate sodium
- 20500 IU for 1 mg of Colistin sulfate
- 820 IU for 1 mg of Dihydrostreptomycin
- 920 IU for 1 mg of Erythromycin
- 620 IU for 1 mg of Gentamicin
- 755 IU for 1 mg for Neomycin
- 8403 IU for 1 mg of Polymyxin B
- 3200 IU for 1 mg of Spiramycin

These coefficients are applied to sales from 1999 to 2014.

Breakdown by species

The interpretation of sales figures by species is made difficult by the fact that the same veterinary medicinal product may be intended for several animal species. It is therefore necessary to make an estimate of sales by species.

Since the 2009 sales survey, MA holders have been asked to provide an estimate of the breakdown by target species for each drug.

This estimate has been provided for all medicinal products.

d) Expression of results

To correctly interpret the data in this report, it is necessary to understand what information is used as a basis for the calculations of the proposed indicators. Several indicators are proposed because the results of this study may be used for different purposes.

Some indicators may be preferred for assessing the correlation between sales of antimicrobials and antimicrobial resistance. Others will be more appropriate for monitoring global changes over time in prescription of veterinary medicinal products and for attempting to measure the impact of actions implemented at national level.

For more details concerning the calculation of the various indicators, an indicator calculation guide is provided in Annex B of this report.

Information used to calculate the indicators

All the indicators are calculated using some or all of the following information:

- Quantity of active ingredient,
- Dosage,
- Duration of treatment,
- Weight of treated animals,
- Weight of adult animals or body weight at slaughter.

These indicators can be calculated for all animal species, by species, by route of administration, by class of antimicrobials.
In this study, the following information has been used:

- **Quantity of active ingredient:** calculated from sales figures for presentations of veterinary medicinal products and their quantitative composition in antimicrobials.

- **Dosage:** the dosage used is that from the MA. When multiple doses are possible, the highest dose is chosen, for the drug's main indication.

- **Duration of treatment:** the duration of treatment used is that from the MA. When multiple treatment durations are possible, the longest treatment duration is chosen, for the drug's main indication.

- **Weight of the animal population:** the weights used correspond to the weights of adult animals for those with a life cycle of more than one year, and to the body weights at slaughter for others.

- **Weight of animals at the time of treatment:** currently, this weight is only taken into account in special cases when more detailed observations are needed. The weights at treatment chosen come from field surveys conducted by ANSES (for the study of exposure to newer-generation cephalosporins in pigs) or weights recorded in pharmacovigilance reports (for the study on exposure to antimicrobials in veal calves).

Indicators of antimicrobial sales

1. Numerators used in the national sales monitoring plan

✓ QAI: the quantity of active ingredient in a unit of weight (mg, kg, tonne or international unit of activity) is easily deduced from sales of commercial units (boxes, cans, bottles, etc.). The active ingredient composition of each commercial unit is multiplied by the number of units sold (from national monitoring of sales) to obtain the corresponding weight of active ingredient.

✓ The ADDkg (Animal Daily Dose) is the dose needed to treat one kilogram of body weight during one day. A corresponding number of ADDkg is calculated by dividing the quantity of active ingredient by the value selected for the ADDkg (daily dosage from the MA under national monitoring of antimicrobial sales).

✓ The ADD (Animal Daily Dose) is the dose required to treat a typical animal for one day.

✓ The ACDkg (Animal Course Dose) = WAT (Weight of animals treated) is the dose required to treat one kilogram of body weight over the entire duration of treatment. A corresponding number of ACDkg is calculated by dividing the quantity of active ingredient by the value selected for the ACDkg (daily dose and duration of treatment from the MA under national monitoring of antimicrobial sales).

✓ The ACD (Animal Course Dose) is the dose required to treat a typical animal for the entire duration of treatment.

2. Denominator used in the national sales monitoring plan

The denominator should represent the population of users or potential users of antimicrobials. The denominator enables population changes over time to be taken into account. The denominator used for the national monitoring of antimicrobial sales is the weight of animals potentially treated with antimicrobials (kg produced). The principle usually chosen is based on the assumption that all the quantities of antimicrobials sold are administered to animals, and therefore that the denominator corresponds to the entire animal population present during the year on the national territory.

For some specific analyses, such as estimating the number of calves treated orally or estimating the number of pigs treated with newer-generation cephalosporins, the denominator is the number of animals potentially treated with antimicrobials.

3. Indicators

✓ Amount of active ingredient in mg of active ingredient per kg of body weight produced: by dividing the weight of active ingredient by the animal mass potentially treated with

antimicrobials, we obtain a quantity of active ingredient expressed in milligrams per kilogram of body weight.

- ✓ ALEA: by dividing the body weight treated (number of ACDkg) by the animal mass that could potentially be treated with antimicrobials, we obtain an expression of sales in ALEA (Animal Level of Exposure to Antimicrobials), the exposure indicator used by ANSES-ANMV.

e) Important points concerning the 2014 survey

The ALEA (Animal Level of Exposure to Antimicrobials) is calculated by taking into account differences in potency and dosage between antimicrobials as well as the changes in the animal population. It is based on the assumption that all the antimicrobials sold during a given year were administered to animals in France during this year.

If the ALEA is calculated this year on the basis of the tonnage of antimicrobials sold, an increase of 13.1% can be observed compared to 2013. Assuming that there was stockpiling by the players involved in distributing and/or prescribing veterinary medicinal products, it is not possible to interpret the observed increase in exposure.
It would therefore be inappropriate this year to conduct a detailed study of ALEAs by species and class of antimicrobials for 2014. The ALEAs by class of antimicrobials and by species will not be presented in the framework of this report, with the exception of those for third- and fourth-generation cephalosporins and fluoroquinolones, for which the observed decline reflects a decrease in use despite any potential stockpiling that may have taken place.

The report on next year's sales will calculate exposure by taking into account the sales data for the two years 2014 and 2015, in order to even out any possible stockpiling phenomenon.

Some dosages and treatment durations used to calculate the body weight treated have been revised and applied to earlier years.

The body weight of broiler chickens (previously set at 1.2 kg) has been upgraded to 1.8 kg, a weight more consistent with reality. This new value has been applied to all the years.

IV. Results for 2014

1. Breakdown presented by antimicrobial class and route of administration

- Results expressed in weight of active ingredient

Table 1. Breakdown of sales (tonnage) of active ingredient for each antimicrobial class by route of administration*

	MEDICATED PREMIXES	ORAL FORMS EXCLUDING PREMIXES	INJECTIONS	INTRAMAMMARY & INTRAUTERINE	TOTAL	PERCENTAGE
AMINOGLYCOSIDES	11.39	10.35	34.54	1.33	57.60	7.37%
OTHER CLASSES[8]	-	1.88	0.05	0.17	2.10	0.27%
CEPHALOSPORINS 1&2G	-	5.39	0.06	1.78	7.23	0.93%
CEPHALOSPORINS 3&4G	-	-	1.59	0.41	2.00	0.26%
FLUOROQUINOLONES	-	2.60	2.29	-	4.89	0.63%
LINCOSAMIDES	1.83	1.98	0.72	0.06	4.59	0.59%
MACROLIDES	11.76	33.26	13.30	0.07	58.39	7.47%
PENICILLINS	12.62	49.40	33.34	2.79	98.15	12.56%
PHENICOLS	-	0.19	5.69	-	5.88	0.75%
PLEUROMUTILINS	2.96	3.45	0.03	-	6.44	0.82%
POLYMYXINS	18.90	31.86	0.55	0.11	51.43	6.58%
QUINOLONES	0.38	5.19	-	-	5.57	0.71%
SULFONAMIDES	63.05	79.00	4.99	-	147.03	18.81%
TETRACYCLINES	135.86	160.28	9.63	1.67	307.44	39.34%
TRIMETHOPRIM	10.16	11.84	0.75	-	22.75	2.91%
TOTAL	268.91	396.68	107.52	8.36	781.50	100.00%
PERCENTAGE	34.41%	50.76%	13.76%	1.07%	100.00%	

* Sales of antimicrobials administered in local forms (sprays, creams, ear or eye solutions) are not presented in this report. They account for less than 0.5% of the tonnage of active ingredient sold.

In 2014, the total volume of sales amounted to 781.50 tonnes of antimicrobials. Sales were distributed unevenly among the 15 classes of antimicrobials, since six classes of antimicrobials (tetracyclines, sulfonamides, penicillins, macrolides, aminoglycosides and polymyxins) accounted for more than 92% of total sales of antimicrobials. Tetracyclines alone represented more than 39% of tonnage sold. Critical antimicrobials (newer-generation cephalosporins and fluoroquinolones) accounted for less than 0.9% of the tonnage of active ingredient sold.

[8] Other classes: clavulanic acid, dimetridazole, metronidazole, pyrimethamine, rifaximin

2. Breakdown by species

- Results expressed in weight of active ingredient

Table 2. Breakdown of sales for 2014 between the different species in tonnage of active ingredient and quantity of active ingredient per animal kg

	Cattle	Cats & Dogs	Horses	Fish	Rabbits	Sheep & Goats	Pigs	Poultry	Other	Total
Tonnage sold	179.78	17.65	15.68	2.12	61.66	46.95	278.15	177.19	2.30	781.50
Percentage	23.0%	2.3%	2.0%	0.3%	7.9%	6.0%	35.6%	22.7%	0.3%	100.0%
Sales in mg/kg	19.11	110.66	53.04	52.08	595.22	80.93	97.53	78.06	65.98	49.63

According to the information on the breakdown by species transmitted to ANSES-ANMV by the pharmaceutical companies, around 36% of the tonnage of antimicrobials sold is intended for pigs, 23% is intended for cattle and around 23% is destined for poultry.

In 2014, 49.63 mg of antimicrobials were sold per kilogram of body weight, with differences depending on the species.

When expressed in weight of active ingredient, the results are not representative of the “exposure” to antimicrobials of the animal species.

V. Change in antimicrobial sales between 1999 and 2014

1. Change in sales by pharmaceutical form

- Results expressed in weight of active ingredient

See Table 3. Change in the weight of active ingredient by pharmaceutical form (in tonnes)

Over 16 years of monitoring, the tonnage of antimicrobials sold has fluctuated between 699.09 and 1383.65 tonnes.
The tonnage of antimicrobials sold in 2014 was higher than that of the previous year. The total sold in 2014 increased by 11.8% compared to the total sold in 2013 but has declined by 23.0% over the last five years. The decrease observed over the last five years is largely attributable to lower sales of orally administered antimicrobials, and medicated premixes in particular.

2. Change in sales and exposure to antimicrobials by class

See Table in the Annex. Change in the mass of the animal population by species from 1999 to 2014 in tonnes (Annex A, Table A2)

See Table 4. Change in sales by class in tonnage of active ingredient sold (in tonnes)

Table 3. Change in the weight of active ingredient by pharmaceutical form (in tonnes)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
MEDICATED PREMIXES	853.26	878.05	821.24	732.31	687.18	650.55	652.56	626.16	712.16	626.55	535.11	494.96	406.69	303.90	258.15	268.91
ORAL POWDERS AND SOLUTIONS	284.61	331.51	383.59	430.96	450.67	464.90	495.34	459.45	473.87	404.73	392.95	388.01	369.15	345.42	313.94	376.83
OTHER ORAL FORMS	20.18	19.43	19.29	18.66	18.58	18.97	20.18	21.43	20.91	21.39	19.50	20.10	19.69	18.77	17.78	20.25
INJECTIONS	138.98	139.53	137.06	131.05	123.93	114.42	116.34	120.10	110.05	108.73	101.70	101.86	104.12	104.70	100.86	107.12
INTRAMAMMARY & INTRAUTERINE	14.25	15.13	13.68	13.63	13.49	11.82	11.71	10.58	10.92	10.99	9.60	9.77	10.11	9.05	8.36	8.39
TOTAL	1,311.29	1,383.65	1,374.86	1,326.60	1,293.84	1,260.66	1,296.14	1,237.71	1,327.92	1,172.38	1,058.86	1,014.69	909.76	781.84	699.09	781.50

Table 4. Change in sales by class in tonnage of active ingredient sold (in tonnes)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
AMINOGLYCOSIDES	81.73	89.56	92.51	90.12	81.66	78.59	76.70	77.64	74.29	72.94	64.88	62.49	63.64	57.37	54.40	57.60
OTHER CLASSES	1.65	1.64	1.53	1.53	0.93	1.46	1.51	2.13	1.93	2.00	1.89	1.99	1.91	1.75	1.73	2.10
CEPHALOSPORINS 1&2G	5.25	5.30	5.24	6.19	6.84	6.71	7.13	6.41	7.16	7.20	7.01	5.94	7.04	6.64	6.40	7.23
CEPHALOSPORINS 3&4G	0.92	1.05	1.02	1.17	1.27	1.37	1.60	1.87	2.00	2.12	1.82	2.28	2.31	2.33	2.13	2.00
FLUOROQUINOLONES	3.30	3.69	4.06	4.18	4.43	4.28	4.36	4.81	4.68	4.89	4.89	5.19	5.23	4.92	4.76	4.89
LINCOSAMIDES	5.88	8.02	9.27	10.85	10.21	9.50	10.06	8.98	9.07	7.79	7.11	6.72	5.43	4.69	4.58	4.59
MACROLIDES	79.42	88.27	101.88	108.23	101.93	96.53	99.88	102.69	97.60	94.89	83.39	81.36	70.44	61.00	51.94	58.39
PENICILLINS	90.46	96.77	94.36	97.54	91.94	84.37	88.70	92.69	93.59	85.04	86.67	90.63	90.25	86.19	86.62	98.15
PHENICOLS	4.31	4.65	4.44	5.61	4.30	4.90	4.69	6.08	5.88	5.01	4.79	5.12	4.57	4.65	4.69	5.88
PLEUROMUTILINS	31.14	32.96	25.80	25.26	21.94	16.15	8.27	10.02	9.95	7.90	8.19	7.62	6.77	5.64	5.64	6.44
POLYMYXINS	67.19	70.44	72.03	67.89	67.30	63.07	66.35	66.80	73.83	65.73	66.40	65.04	60.72	51.31	42.82	51.43
QUINOLONES	19.75	16.50	14.86	15.82	13.99	12.50	13.29	13.04	10.91	7.93	7.48	8.03	6.24	5.35	4.70	5.57
SULFONAMIDES	259.06	270.51	245.47	228.42	208.90	209.64	215.15	211.30	224.50	194.83	181.21	174.00	170.67	145.30	136.27	147.03
TETRACYCLINES	623.82	655.70	666.22	629.91	645.70	637.81	662.93	600.14	678.70	584.57	504.97	471.98	389.62	323.42	272.21	307.44
TRIMETHOPRIM	37.42	38.59	36.19	33.88	32.51	33.77	35.53	33.12	33.82	29.55	28.16	26.29	24.91	21.27	20.21	22.75
TOTAL	1,311.29	1,383.65	1,374.86	1,326.60	1,293.84	1,260.66	1,296.14	1,237.71	1,327.92	1,172.38	1,058.86	1,014.69	909.76	781.84	699.09	781.50

3. Change in antimicrobial sales by species

The results presented by species are expressed in weight of active ingredient and quantity of active ingredient divided by the weight of the animal population.

3.1. Results for cattle

See Table 5. Change in sales for cattle

Between 1999 and 2005, the weight of active ingredient sold for treating cattle increased considerably; it then declined to reach its lowest level in 2013, before increasing by 22.2% in 2014.

3.2. Results for domestic carnivores

See Table 6. Change in sales for domestic carnivores

Between 1999 and 2007, there was an increase in the tonnage of antimicrobials sold intended for cats and dogs. It then declined between 2008 and 2013. In 2014, the tonnage sold increased by 16.4% compared to 2013.

3.3. Results for rabbits

See Table 7. Change in sales for rabbits

The tonnage intended for rabbits increased between 1999 and 2004, remained stable between 2004 and 2007, and then declined considerably between 2007 and 2013 (the tonnage fell by half over this period). Between 2013 and 2014, the tonnage sold increased by 17.5%.

3.4. Results for pigs

See Table 8. Change in sales for pigs

The tonnage of antimicrobials sold for treating pigs in 2014 increased by 6.1% compared to the tonnage sold in 2013.

3.5. Results for poultry

See Table 9. Change in sales for poultry

The tonnage intended for poultry increased between 1999 and 2002, remained stable between 2003 and 2007, and then declined between 2007 and 2013, before increasing again between 2013 and 2014 (+13.2%).

Table 5. Change in sales for cattle

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Tonnage sold	169.4	179.1	175.2	176.0	172.7	194.3	207.3	200.9	199.0	183.8	173.0	182.8	183.5	166.1	147.2	179.8
Percentage of total tonnage	12.9%	12.9%	12.7%	13.3%	13.3%	15.4%	16.0%	16.2%	15.0%	15.7%	16.3%	18.0%	20.2%	21.2%	21.1%	23.0%
Quantity in mg/kg	16.29	17.11	16.30	16.86	17.30	19.72	22.34	21.02	20.59	18.74	17.79	19.11	19.65	17.93	15.76	19.11

Table 6. Change in sales for domestic carnivores

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Tonnage sold	16.0	15.9	15.7	16.5	15.6	16.6	17.7	19.1	19.1	19.1	18.3	17.9	17.7	16.5	15.2	17.7
Percentage of total tonnage	1.2%	1.1%	1.1%	1.2%	1.2%	1.3%	1.4%	1.5%	1.4%	1.6%	1.7%	1.8%	1.9%	2.1%	2.2%	2.3%
Quantity in mg/kg	102.35	100.79	92.52	97.11	92.83	99.32	105.48	118.45	118.55	119.59	114.56	113.70	112.38	105.19	96.68	110.60

Table 7. Change in sales for rabbits

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Tonnage sold	75.4	82.5	80.8	89.8	100.5	116.8	114.8	103.2	113.7	103.0	88.2	79.9	71.1	55.3	52.5	61.7
Percentage of total tonnage	5.8%	6.0%	5.9%	6.8%	7.8%	9.3%	8.9%	8.3%	8.6%	8.8%	8.3%	7.9%	7.8%	7.1%	7.5%	7.9%
Quantity in mg/kg	542.69	605.43	595.30	662.34	779.80	897.94	897.44	831.33	905.19	919.87	859.86	799.71	659.44	535.93	517.57	595.22

Table 8. Change in sales for pigs

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Tonnage sold	652.4	694.0	696.4	654.7	621.6	575.4	595.5	575.9	635.8	537.1	484.1	446.9	354.4	287.4	262.1	278.1
Percentage of total tonnage	49.7%	50.2%	50.7%	49.4%	48.0%	45.6%	45.9%	46.5%	47.9%	45.8%	45.7%	44.0%	39.0%	36.8%	37.5%	35.6%
Quantity in mg/kg	203.97	215.42	216.29	201.61	193.47	181.36	191.49	186.63	205.08	173.25	158.70	147.60	118.20	98.40	91.31	97.53

Table 9. Change in sales for poultry

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Tonnage sold	221.4	237.2	249.3	251.0	261.9	251.3	254.6	237.7	254.4	242.2	216.4	203.4	202.0	176.6	156.6	177.2
Percentage of total tonnage	16.9%	17.1%	18.1%	18.9%	20.2%	19.9%	19.6%	19.2%	19.2%	20.7%	20.4%	20.0%	22.2%	22.6%	22.4%	22.7%
Quantity in mg/kg	76.14	80.92	82.10	89.85	95.15	95.03	99.17	102.02	104.39	101.38	92.89	86.12	84.65	75.32	67.31	78.06

VI. Update on exposure to fluoroquinolones and third- and fourth-generation cephalosporins

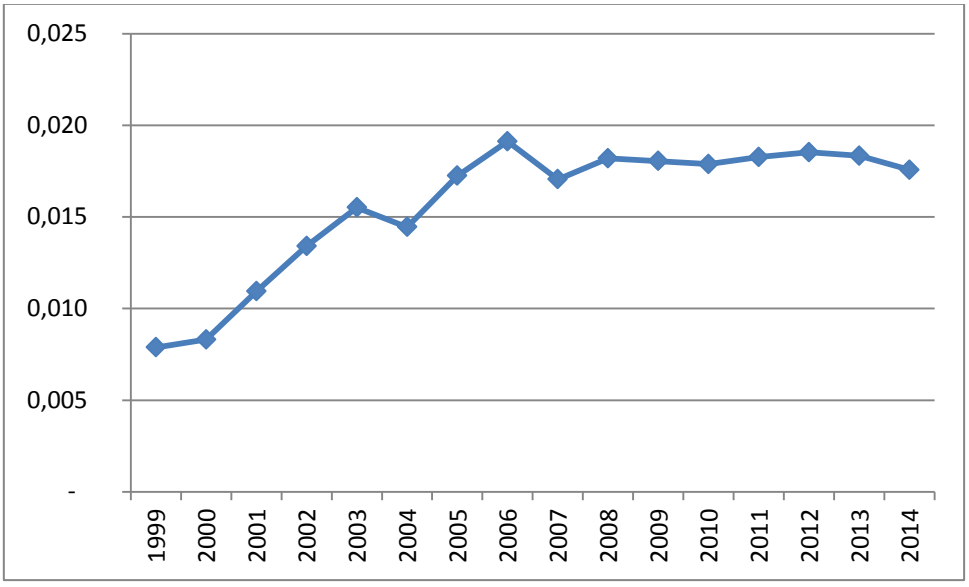
1. *Fluoroquinolones*

In 1999, 18 drugs containing a fluoroquinolone had marketing authorisation. In 2014, this number had risen to 117.
In veterinary medicine, seven active ingredients are sold belonging to the class of fluoroquinolones (danofloxacin, difloxacin, enrofloxacin, ibafloxacin, marbofloxacin, orbifloxacin and pradofloxacin). The tonnages of fluoroquinolones used in veterinary medicine are quite low (0.25% of the tonnage of active ingredient sold in 1999 and 0.63% of the tonnage sold in 2014) but expressing sales as body weight treated reveals the non-negligible use of this class (2.0% of body weight treated in 1999 and 4.1% of body weight treated in 2014, with differences depending on species and route of administration).

All species and routes of administration combined, there has been a trend towards stabilisation of exposure in recent years.

Over the last five years, the indicator of exposure to fluoroquinolones has decreased (a fall of 4.1% over the last five years). Between 2013 and 2014, all animal species combined, the indicator of exposure to fluoroquinolones declined (-3.5%).

Figure 1. Change in exposure to cephalosporins (ALEA)



When considering the change in exposure more precisely, a different trend can be seen depending on the target species and routes of administration.

Fluoroquinolones are authorised only for cattle (oral and parenteral route), cats and dogs (oral and parenteral), pigs (parenteral), poultry (oral) and rabbits (oral). According to the reports submitted by

the pharmaceutical companies, fluoroquinolones are also used in the horse sector. Off-label uses not quantified by the pharmaceutical companies as part of this monitoring have not been considered.

Figure1a. Tonnage of body weight treated parenterally with fluoroquinolones

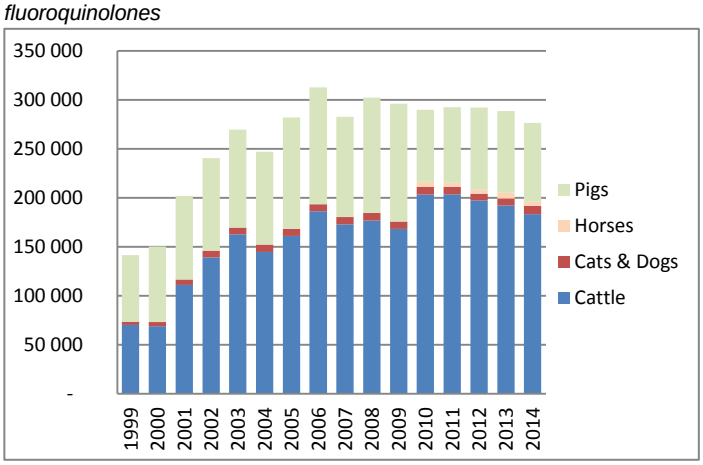


Figure1b. Tonnage of body weight treated orally with fluoroquinolones

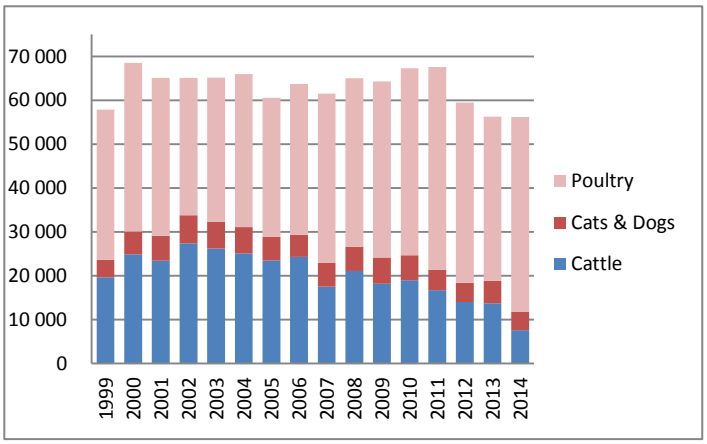


Figure1c. Tonnage of body weight of cattle treated parenterally with fluoroquinolones

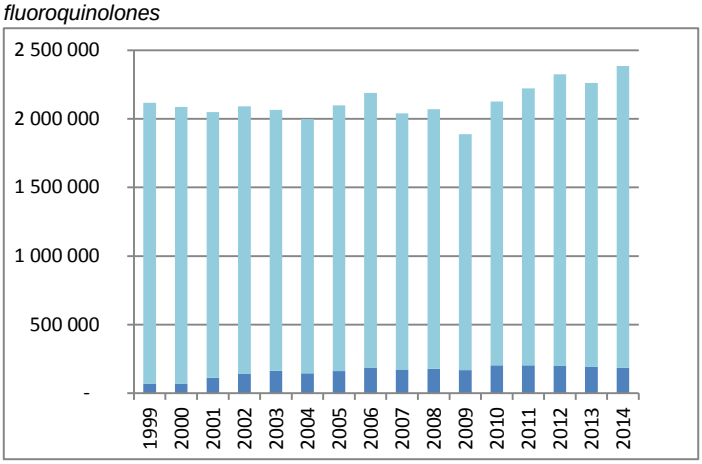


Figure1d. Tonnage of body weight of cattle treated orally with fluoroquinolones

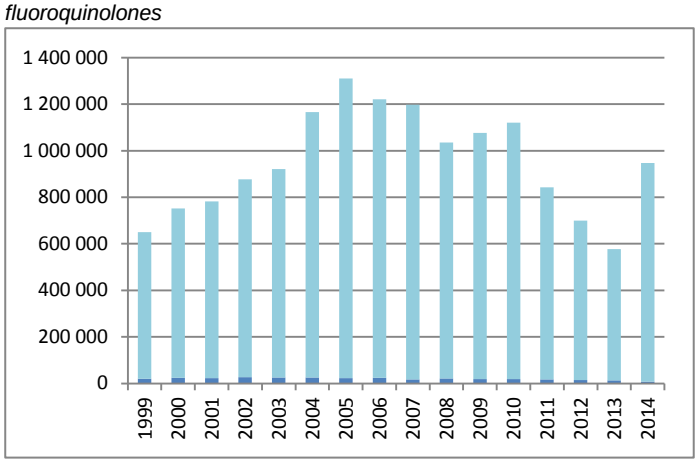


Figure1e. Tonnage of body weight of cats and dogs treated parenterally with fluoroquinolones

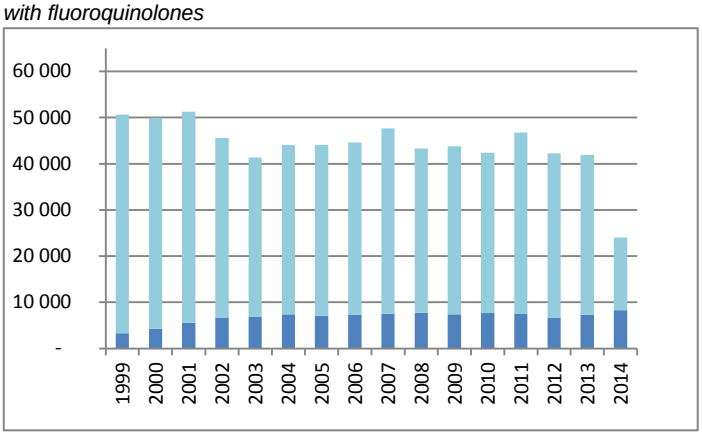


Figure1f. Tonnage of body weight of cats and dogs treated orally with fluoroquinolones

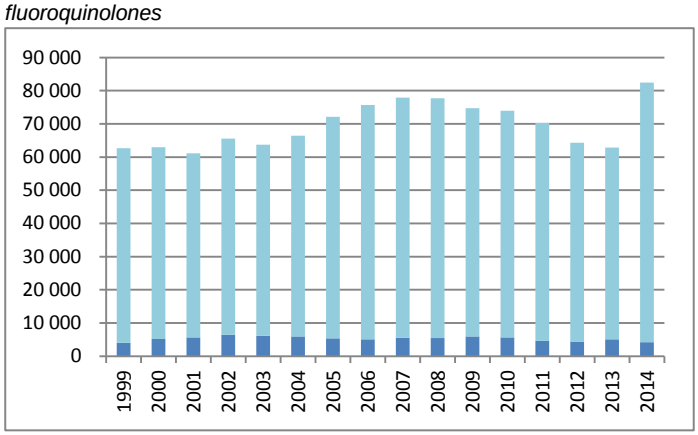


Figure1g. Tonnage of body weight of pigs treated parenterally with fluoroquinolones

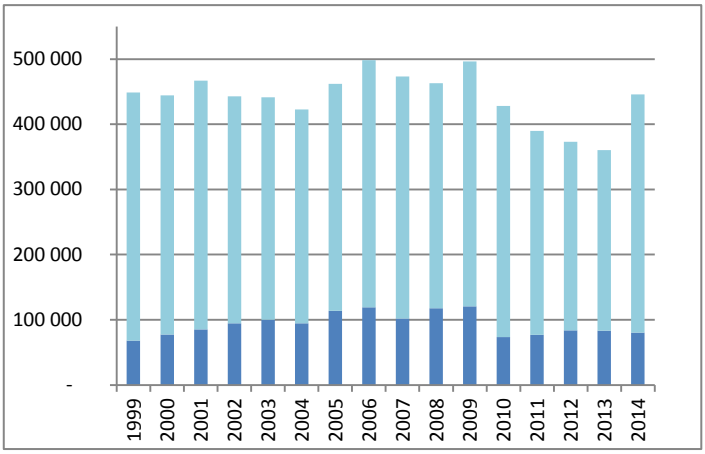
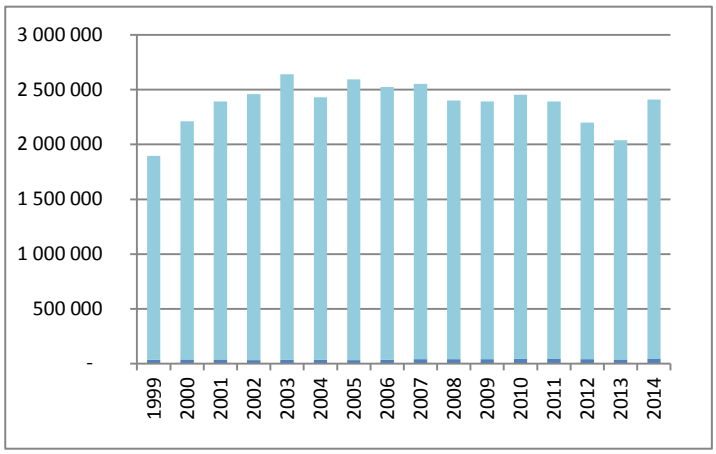


Figure1h. Tonnage of body weight of poultry treated orally with fluoroquinolones



Legend to figures 1c to 1h:

	Other classes
	Fluoroquinolones

- Change in body weight of animals treated parenterally with fluoroquinolones

After a period of stability in the body weight treated with fluoroquinolones by the parenteral route between 2010 and 2013, 2014 was marked by a fall in the body weight treated by this class of antimicrobials.

Between 1999 and 2010, a large increase was observed in parenteral treatments based on fluoroquinolones in the cattle sector. A certain stability was observed between 2010 and 2013, followed by a decrease of 4.7% in 2014 compared to the previous year.
The parenteral use of fluoroquinolones in pigs increased until 2009, since when it has remained relatively stable. A fall between 2013 and 2014 should be noted (-3.7%).
In 2014, fluoroquinolones accounted for 7.7% of the body weight of cattle treated parenterally, 34.4% of the body weight of domestic carnivores treated parenterally and 18.0% of the body weight of pigs treated parenterally.

- Change in body weight of animals treated orally with fluoroquinolones

Between 2011 and 2013, for the oral route, there was a decrease in body weight treated. Between 2013 and 2014 the body weight treated orally with fluoroquinolones remained stable. Oral treatments based on fluoroquinolones in poultry increased continuously between 2005 and 2011, and then decreased between 2011 and 2013. However, the body weight treated in 2014 increased by 15.7% compared to 2013. For cattle, the use of this class of antimicrobials by the oral route has fallen since 2008, with this decline being particularly sharp between 2013 and 2014 (-81.1%).

In 2014, fluoroquinolones accounted for 0.8% of the body weight of cattle treated orally, 5.1% of the body weight of domestic carnivores treated orally, and 1.8% of the body weight of poultry treated orally.

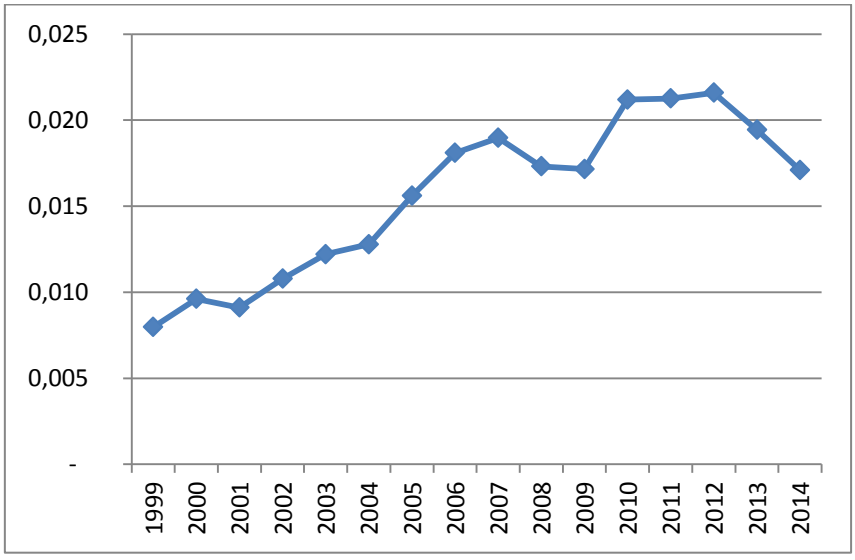
2. *Newer-generation cephalosporins*

In 1999, six drugs containing a newer-generation cephalosporin were on the market in France. In 2014, 29 drugs containing a newer-generation cephalosporin were available on the market.
In veterinary medicine, four active ingredients (cefovecin, cefoperazone, cefquinome and ceftiofur) belonging to the third- and fourth-generation cephalosporins are sold. The tonnages of third- and fourth-generation cephalosporins used in veterinary medicine are low (0.1% of the tonnage of active ingredient sold in 1999 and 0.3% of the tonnage sold in 2014) but expressing sales as body weight treated reveals the non-negligible use of this class (1.4% of body weight treated in 1999 and 2.8% of body weight treated in 2014, with differences depending on species).

All species combined[9], a stabilisation in exposure has been observed between 2010 and 2012 and a significant fall since 2012 (-20.8% between 2012 and 2014).

Over the last five years, the indicator of exposure to third- and fourth-generation cephalosporins has fallen by 19.3%. Following a period of stabilisation between 2010 and 2012, a fall in the indicator of exposure to cephalosporins (-12.0% between 2013 and 2014) has since been observed.

Figure 2. Change in parenteral exposure to cephalosporins (ALEA)

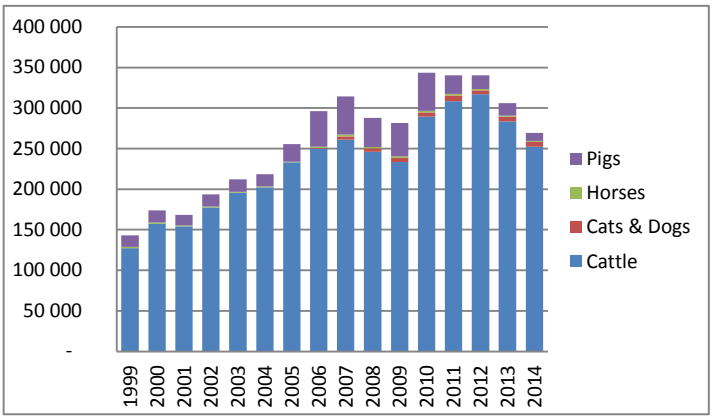


When considering the change in exposure more precisely, a different trend can be seen depending on the target species and routes of administration.

Newer-generation cephalosporins are authorised only for the intramammary route in cattle, and the parenteral route in cattle, cats and dogs, horses and pigs. Off-label uses not quantified by the pharmaceutical companies as part of this monitoring have not been considered.

[9] Exposure to newer-generation cephalosporins via the intramammary route is not presented in this report

Figure 2a. Tonnage of body weight treated parenterally by third- and fourth-generation cephalosporins



In 2014, more than 93% of body weight treated by newer-generation cephalosporins was in the cattle sector.

Figure 2b. Tonnage of body weight of cattle treated parenterally with newer-generation cephalosporins

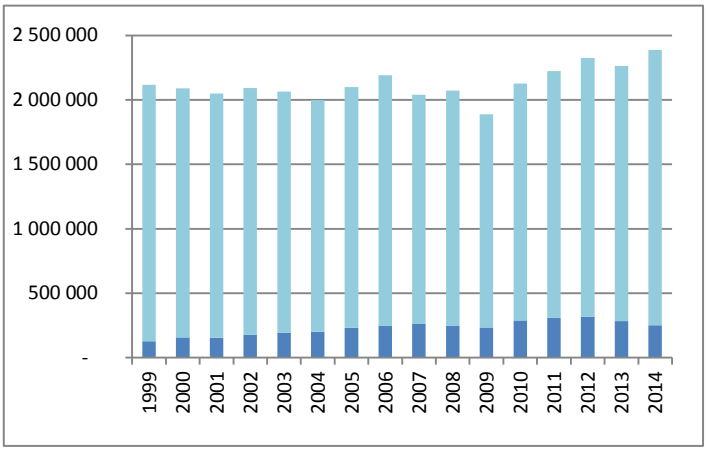


Figure 2c. Tonnage of body weight of cats and dogs treated parenterally with newer-generation cephalosporins

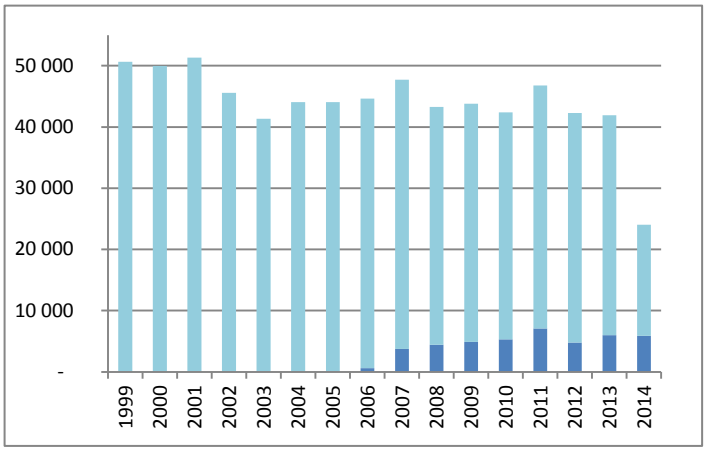
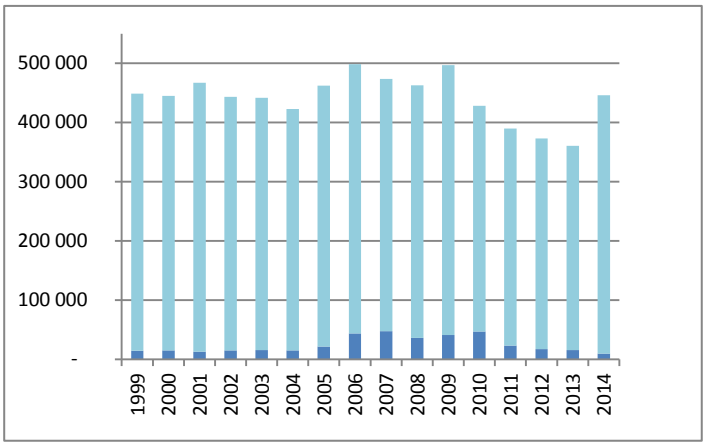


Figure 2d. Tonnage of body weight of pigs treated parenterally with newer-generation cephalosporins



Legend to figures 2b, 2c, 2d:

	Other classes
	Cephalosporins 3 & 4G

In 2014, newer-generation cephalosporins accounted for 10.6% of the body weight of cattle treated parenterally and 24.6% of the body weight of domestic carnivores treated parenterally.

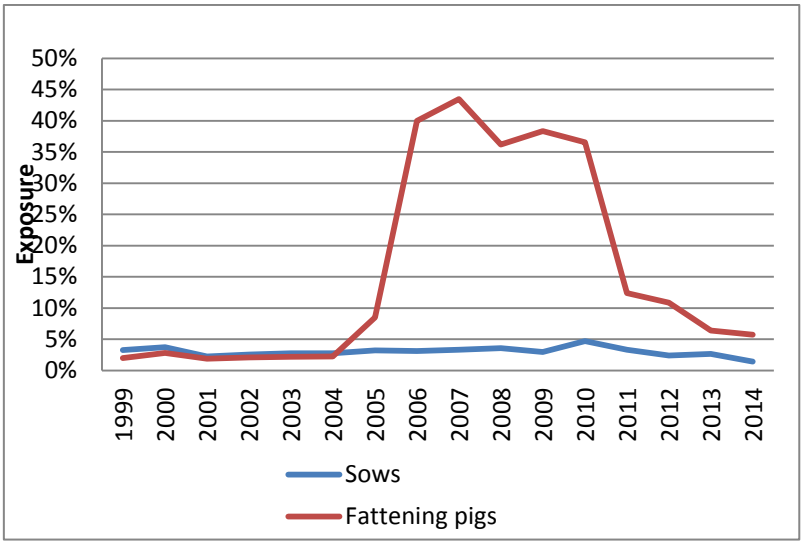
- Change in the number of pigs treated with newer-generation cephalosporins since 1999

At the end of 2010, the pig sector took the initiative to limit the use of newer-generation cephalosporins. In line with this decision by the sector, the ALEA for pigs to ceftiofur and cefquinome fell by 78.2% between 2010 and 2014.

Taking into account the body weight treated as assessed by ANSES-ANMV and the weight of the animals at the time of treatment (information from surveys conducted by ANSES Ploufragan), it is possible to estimate the number of animals treated. By relating the number of animals treated to the target population, we can obtain an estimate of the percentage of animals treated.

According to the field surveys, third- and fourth-generation cephalosporins are used in piglets, fattening pigs and sows. The surveys also provided an idea of the breakdown of sales intended for different categories of animals, once the number of treated animals could be estimated.

Figure 3. Change in the estimated number of pigs treated with cephalosporins



While the initiative restricting the use of newer-generation cephalosporins does not seem to have fundamentally brought about a change of use in sows, there has been a considerable decrease in their use in growers. According to our estimates, based on information from breeder surveys conducted by ANSES Ploufragan, while 36.5% of growers were treated with newer-generation cephalosporins in 2010, in 2014, just 5.7% of them received a treatment based on ceftiofur or cefquinome. There was therefore a 84.3% decrease in the estimated percentage of animals treated between 2010 and 2014.

In 2014, newer-generation cephalosporins accounted for 2.2% of the body weight of pigs treated parenterally. In 2010, this same class represented 11.0% of the body weight of pigs treated parenterally. The initiative in the pig sector to voluntarily restrict the use of newer-generation cephalosporins has led to a sharp fall in the use of this class (see VI.4. Results for pigs).

VII Discussion

The results of this survey should be used with caution. In this report, different indicators have been used to describe different phenomena. It is very important to choose the most appropriate indicator to describe a specific change.

Antimicrobial sales expressed in weight of active ingredient do not reflect exposure to the different classes because the antimicrobials' therapeutic activity is not taken into account. This may be of interest for environmental studies.

It is therefore necessary to distinguish between indicators of "sales" (in mg of active ingredient and mg/kg, i.e. mass of active ingredient relative to the weight of the animal population) and indicators of exposure (ADDkg, ACDkg, ALEA).

Expressing sales in terms of the quantity of active ingredient is an accurate measurement when applied to all species combined. When it is defined by species, it is based on an estimate of the breakdown of sales between different species potentially treated with antimicrobials and becomes an estimated measurement. All expressions of sales in terms of exposure indicators are estimated measurements. They result from the pharmaceutical companies' estimates of the breakdown of sales by species, and dosages and durations of treatment specified by the MA that are sometimes unrelated to the dosages and durations actually applied in the field.

Since 2009, the breakdown between different species has been based on information provided by the MA holders. This information has been provided for all drugs intended for more than one target species.

The methodology used in this survey of sales of antimicrobials cannot accurately describe off-label use, even though the new approach introduced in 2009 (estimation by MA holders of the breakdown by species) partly takes this type of use into account. The need for more precise data on the use of antimicrobials by species and category of animals is regularly reiterated at European level. Initiatives are under way to improve the estimation of exposure to antimicrobials by category of animals, physiological stage or species (for poultry). The measures in Axis 4 of the national plan to reduce the risks of antimicrobial resistance in veterinary medicine, which include conducting surveys by sector, will provide some answers in the near future to improve the documenting of actual use in the production sectors.

The availability of more precise data on prescription/issuance or use would yield data on the quantities actually administered to animals and make it possible to quantify more precisely any possible stockpiling of medicines in 2014.

Regarding the volume of antimicrobials sold in France, the results show an increase of 11.8% in the tonnage sold between 2013 and 2014. Despite this increase, the tonnage sold in 2014 has still fallen by 23.0% compared to 2010.

The increase in sales should be seen in the context of the publication of Act no. 2014-1170 of 13 October 2014 on the future of agriculture, food and forestry, which includes several measures, such as an end to discounts, rebates and reductions with effect from 1 January 2015.
This legislative change may have led to stockpiling of medicines containing antimicrobials among the parties involved in the distribution and/or prescription of veterinary medicinal products during 2015.

It is usually considered that sales of medicinal products over a given year reflect exposure of animals for the same year. Given the assumptions made about drug stockpiling, this premise is not valid for 2014.

This year, the exposure indicators used are probably not representative of the exposure of animals to antimicrobials and may instead reflect varying degrees of accumulation of certain drugs intended for certain species.

This stockpiling is estimated to cover approximately 3 to 4 months, which would lead to an overestimation of exposure for 2014 and an underestimation of animal exposure in 2015. The data on turnover from sales of antimicrobials[10] confirms this analysis, since after the increase observed for 2014, there was a decline in turnover of antimicrobials for the first half of 2015 compared to the first half of 2014.

Third- and fourth-generation cephalosporins and fluoroquinolones are considered as particularly important in human medicine because they are among the only alternatives for the treatment of certain infectious diseases in humans. These two classes of compound have been available in veterinary medicine for the last fifteen or so years. According to European recommendations, these antimicrobials should be reserved for second-line therapeutic treatment. In 2006, in its report entitled “Veterinary use of antimicrobials, bacterial resistance and consequences for human health”, ANSES warned of the need to reduce the use of antimicrobials as a preventive treatment, and to monitor in particular these two classes of antimicrobials and resistance to them. In previous reports on this annual monitoring of antimicrobial sales, ANSES also mentioned the disturbing increase in the use of these two classes of antimicrobials. More recently, the report published by ANSES in 2014 on "The risk of emergence of antimicrobial resistance associated with patterns of antimicrobial use in the field of animal health" reinforces and clarifies this message.

Exposure of animals to critical antimicrobials (third- and fourth-generation cephalosporins and fluoroquinolones), after stabilising, has been falling over the past few years. The classes of critical antimicrobials are the only two classes of antimicrobials for which sales decreased between 2013 and 2014.

[10] Figures from the French Industry Association for the Study of Veterinary Medicinal Products (AIEMV)

IX. Conclusion

The information gathered by means of this national monitoring scheme is one of the essential elements, together with monitoring of bacterial resistance, needed for assessing the risks associated with antimicrobial resistance.
In France, many measures have been taken since late 2010 to promote the prudent use of antimicrobials:

- initiative in the pig sector on limiting the use of cephalosporins,
- charter on correct use of drug therapies in rabbit farming,
- inter-professional charter on good health management and correct use of drug therapies in veal calf production,
- raising awareness in many sectors about good practice and the rational use of antimicrobials,
- introduction in veterinary medicine of the EcoAntibio 2017 national plan, which aims to reduce use of antimicrobials (all classes combined) by 25% in five years, while preserving the therapeutic arsenal,
- ANSES internal request to assess the risk of emergence of antimicrobial resistance associated with patterns of antimicrobial use in the field of animal health,
- Act no. 2014-1170 of 13 October 2014 on the future of agriculture, food and forestry, which has set a target of a 25% reduction in the use of fluoroquinolones and third- and fourth-generation cephalosporins by December 2016, taking 2013 as the reference year,
- change in commercial policies for purchases and sales of antimicrobials (in the framework of the Act on the future of agriculture).

The end to discounts, rebates and discounts from 1 January 2015 may have had a drug stockpiling effect among the parties involved in the distribution and/or prescription of veterinary medicinal products, which makes it difficult to interpret the various indicators of antimicrobial sales for 2014.

Exposure of animals to critical antimicrobials (third- and fourth-generation cephalosporins and fluoroquinolones), after stabilising, has been falling over the past few years. The classes of critical antimicrobials are the only two classes of antimicrobials for which sales decreased between 2013 and 2014.

The Act on the future of agriculture sets a target for reducing the use of cephalosporins and fluoroquinolones by 25% in three years (taking 2013 as the reference year). Reaching this target will require the implementation of new measures, especially in sectors where the use of these classes of compounds is high.

IX ANNEXES

A. Animal population

Table A1. Parameters for calculating the total body weight of animals potentially treated with antimicrobials between 1999 and 2014

Type/Species	BW in kg	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Pets and sport animals (number of animals)																	
Dogs	15	8,100,000	8,100,000	8,800,000	8,780,000	8,600,000	8,500,000	8,510,000	8,080,000	8,080,000	7,800,000	7,800,000	7,590,000	7,590,000	7,420,000	7,420,000	7,260,000
Cats	4	8,700,000	9,000,000	9,400,000	9,670,000	9,700,000	9,900,000	9,940,000	10,040,000	10,040,000	10,700,000	10,700,000	10,960,000	10,960,000	11,410,000	11,410,000	12,680,000
Birds	0.1	7,100,000	7,000,000	8,100,000	8,000,000	6,700,000	6,600,000	6,590,000	3,680,000	3,680,000	3,500,000	3,500,000	6,040,000	6,040,000	6,430,000	6,430,000	5,750,000
Small mammals	0.5	1,800,000	2,000,000	4,900,000	2,320,000	4,100,000	3,800,000	3,770,000	2,940,000	2,940,000	3,200,000	3,200,000	3,010,000	3,010,000	2,660,000	2,660,000	2,840,000
Sport horses	450	469,664	469,664	471,366	494,658	496,799	500,250	502,148	497,540	503,119	503,085	504,914	509,198	510,618	498,069	489,531	488,734
Draught horses	850	78,122	78,122	77,340	76,777	76,236	76,611	75,140	73,969	73,260	76,558	76,298	73,368	73,314	72,451	72,478	71,659
Donkeys	350	43,202	43,202	46,260	46,929	48,691	48,994	49,696	49,740	48,912	47,911	48,101	49,222	48,222	44,468	44,150	42,173
Sheep - goats (number of animals)																	
Goats	50	1,362,341	1,362,341	*1,373,565*	1,380,109	1,370,811	1,358,242	1,360,945	1,367,788	1,358,729	1,361,983	1,410,567	1,437,620	1,381,209	1,307,753	1,290,623	1,283,128
Kids	9.76	741,132	704,766	*697,977*	725,605	746,987	761,582	913,258	762,212	751,800	707,965	658,507	686,549	707,988	678,094	625,791	589,959
Dairy ewes	60	1,297,000	1,366,038	1,332,571	1,329,870	1,327,743	1,309,756	1,299,846	1,276,350	1,252,817	1,272,811	1,280,508	1,324,055	1,297,651	1,290,933	1,238,433	1,230,484
Meat ewes	80	5,157,000	5,160,188	4,985,757	4,884,497	4,841,187	4,787,806	4,749,568	4,613,460	4,523,942	4,168,244	4,054,899	3,980,852	3,810,524	3,937,647	3,815,385	3,746,623
Covered ewe lambs	45	937,000	1,205,963	1,247,369	1,265,207	1,270,733	1,268,457	1,262,518	1,201,634	1,165,785	1,118,348	1,133,234	1,151,674	1,103,628			
Maiden ewes	20	348,000	329,000	327,000	325,000	346,000	344,000	363,365	331,323	316,372					1,067,159	1,040,389	1,062,014
Lambs	15	5,336,584	5,422,589	5,400,786	5,120,916	5,045,598	4,826,975	4,724,274	4,623,501	4,581,528	4,233,962	3,868,100	3,860,200	3,958,707	3,796,118	3,662,175	3,685,991
Other sheep	45	1,771,000	1,782,514	1,823,812	1,819,113	1,815,842	1,785,370	1,760,340	1,733,031	1,668,163	1,562,301	1,552,740	1,465,573	1,406,231	1,389,970	1,342,897	1,337,497
Cattle (number of animals)																	
Dairy cows	650	4,424,000	4,153,000	4,195,000	4,128,000	4,012,000	3,803,000	3,957,858	3,882,195	3,869,936	3,863,435	3,747,886	3,732,707	3,664,153	3,643,200	3,697,232	3,698,547
Meat cows	750	4,071,000	4,214,000	4,293,000	4,095,000	4,040,000	4,166,000	4,068,096	4,156,628	4,247,432	4,313,976	4,271,801	4,299,792	4,145,382	4,109,861	4,101,296	4,144,051
1 to 2 yr old dairy heifers	350	1,350,846	1,418,000	1,433,000	1,396,000	1,380,000	1,346,000	2,035,440	1,147,598	1,120,796	1,109,701	1,188,085	1,161,313	1,150,334	1,171,956	1,180,161	1,204,827
+ 2 yr old dairy heifers	500	951,154	974,000	1,009,000	1,009,000	1,002,000	982,000		815,049	800,649	778,266	804,095	834,652	805,082	763,931	779,828	782,624
1 to 2 yr old meat heifers	450	980,827	1,044,000	1,085,000	1,009,000	970,000	971,000	1,899,069	1,068,008	1,086,069	1,175,059	1,095,383	1,026,254	942,066	949,755	972,396	945,257
+ 2 yr old meat heifers	550	906,000	943,000	946,000	957,000	918,000	891,000		869,811	891,863	980,352	1,080,162	1,026,119	879,626	852,355	886,555	915,290
1 to 2 yr old other females	400	393,000	303,000	404,000	383,000	334,000	315,000	535,667	270,742	295,220	304,547	294,743	281,584	363,906	369,777	376,364	374,422
+ 2 yr old other females	500	294,000	318,000	320,000	402,000	362,000	327,000		228,202	240,939	248,282	258,280	253,951	330,863	318,016	329,521	337,753
1 to 2 yr old bullocks	575	303,938	315,000	315,000	372,000	302,000	290,000	481,770									
+ 2 yr old bullocks		273,062	283,000	283,000	314,000	304,000	260,000										
Non castrated males	650	971,562	918,000	1,105,438	906,509	754,000	774,000	633,675									
0 to 1 yr old cattle	200	5,169,611	5,706,000	5,612,562	5,494,491	4,961,000	4,994,000	4,611,368	4,947,374	5,002,669	4,989,176	4,816,839	4,838,766	4,887,805	4,899,508	4,812,509	4,921,615
1 to 2 yr old males	400								447,909	453,517	499,047	512,824	502,191	415,745	396,236	409,968	428,443
+ 2 yr old males	700								922,177	951,291	990,268	981,930	709,607	846,860	880,422	908,799	893,747
Veal calves (slaughtered)	150	1,887,941	1,843,013	1,882,763	1,862,961	1,822,579	1,751,708	1,750,492	1,700,867	1,564,548	1,506,004	1,476,889	1,464,660	1,439,099	1,378,467	1,332,592	1,305,502

Table A1 (continued). Parameters for calculating the total body weight of animals potentially treated with antimicrobials between 1999 and 2014

Type/Species	BW in kg	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Poultry (number of slaughtered animals)																	
Female rabbits	4	1,446,000	1,376,000	1,335,000	1,293,000	1,196,000	1,181,000	1,127,000	1,053,000	1,061,000	1,012,000	893,000	878,000	871,000	835,000	825,000	835,000
Rabbits	2.5	42,501,500	41,445,200	41,216,300	40,411,500	38,096,100	39,199,500	38,950,900	38,691,100	39,254,500	37,094,200	35,054,000	34,667,600	33,791,600	37,242,000	36,586,000	37,430,000
Broilers	1.8	777,896,300	734,563,400	782,180,300	729,489,300	739,219,300	694,837,500	715,915,700	636,178,400	699,511,600	711,875,400	718,368,200	740,246,900	781,104,600	767,394,000	790,002,000	745,855,000
Turkeys	10	105,470,400	113,860,700	112,554,300	98,661,300	95,575,100	93,668,900	81,146,300	72,834,400	70,220,900	62,857,200	58,024,100	56,187,900	53,824,600	50,217,000	44,267,000	45,996,000
Ducks	4	69,566,800	73,494,900	79,505,400	79,243,900	73,878,900	73,384,800	76,148,200	74,863,200	79,114,700	79,134,200	75,137,100	77,105,400	79,177,800	77,918,000	74,888,000	76,124,000
Guinea fowl	1.4	32,725,000	34,760,000	36,988,000	31,071,000	29,208,000	29,020,000	29,902,000	27,284,000	28,092,000	27,936,000	27,168,000	26,457,000	26,714,000	24,954,000	24,761,000	25,088,000
Laying hens	2	49,054,000	48,145,000	49,052,000	48,664,000	49,050,000	47,224,000	46,753,000	45,703,000	45,213,000	45,990,000	45,306,000	46,564,000	43,063,000	43,050,000	48,826,000	49,110,000
Pigeons	0.65	4,303,000	4,484,000	4,122,000	4,303,000	3,875,000	3,875,000	4,300,000	3,600,000	3,400,000	3,400,000	3,400,000	11,108,971	11,108,971	11,108,971	11,108,971	11,108,971
Quails	0.5	52,907,000	52,907,000	60,100,000	60,400,000	54,206,000	47,364,000	49,400,000	46,952,000	50,786,000	55,137,000	47,540,000	52,890,000	53,563,000	53,542,000	54,849,000	55,161,000
Geese	8	480,000	612,000	616,000	692,000	645,000	560,000	458,000	469,000	474,000	462,000	448,000	324,000	296,000	295,000	249,000	241,000
Pigs (number of slaughtered animals)																	
Cull animals	350	608,698	580,334	581,548	582,418	541,406	521,412	491,911	484,950	471,395	445,213	423,514	396,998	396,397	384,557	356,481	353,033
Sows (number)	300	1,029,000	1,210,208	1,369,000	1,360,000	1,328,000	1,302,000	1,266,951	1,256,179	1,224,100	1,225,574	1,207,500	1,162,135	1,105,812	1,074,340	1,046,738	1,037,435
Fattening pigs	105	25,490,863	25,291,317	24,815,811	25,102,459	25,000,385	24,757,765	24,359,049	24,184,591	24,457,730	24,539,585	24,192,857	24,189,737	24,073,359	23,464,399	23,161,982	23,019,921
Farmed fish (in kg)																	
Trout		46,160,000	47,500,000	47,500,000	42,900,000	37,000,000	37,500,000	34,000,000	34,000,000	34,000,000	34,000,000	34,000,000	34,000,000	36,000,000	36,000,000	32,000,000	32,000,000
Carp		6,000,000	6,000,000	6,000,000	6,000,000	6,000,000	6,000,000	6,000,000	6,000,000	6,000,000	6,000,000	6,000,000	4,000,000	3,500,000	3,500,000	3,500,000	3,500,000
Salmon					5,000,000	800,000	70,000	1,200,000	1,600,000	1,800,000	-	-	802,000	700,000	300,000	300,000	300,000
Bass		3,150,000	3,600,000	3,000,000	3,500,000	3,700,000	4,000,000	4,300,000	5,585,000	4,764,000	3,968,000	3,204,000	2,779,000	3,000,000	2,300,000	1,970,000	1,970,000
Bream		1,000,000	1,400,000	1,700,000	1,500,000	1,100,000	1,600,000	1,900,000	2,200,000	1,392,000	1,636,000	1,648,000	1,377,000	1,500,000	1,300,000	1,477,000	1,477,000
Turbot		900,000	1,000,000	700,000	750,000	909,000	949,000	791,000	870,000	850,000	850,000	531,000	394,000	300,000	250,000	255,000	255,000

Table A2. Change in the mass of the animal population by species between 1999 and 2014 (in tonnes)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Cattle	10,397,639	10,466,102	10,746,012	10,436,923	9,982,187	9,852,206	9,278,685	9,558,491	9,665,091	9,807,349	9,728,553	9,563,507	9,337,803	9,261,897	9,335,521	9,410,073
Pigs	3,198,285	3,221,768	3,219,902	3,247,604	3,212,933	3,172,660	3,109,954	3,085,968	3,100,280	3,100,153	3,050,730	3,027,512	2,998,185	2,920,659	2,870,798	2,851,884
Poultry	2,907,401	2,931,104	3,036,354	2,793,233	2,753,116	2,644,174	2,566,981	2,329,518	2,436,728	2,388,839	2,329,853	2,361,950	2,386,839	2,345,318	2,325,960	2,269,847
Fish	57,320	59,630	59,050	59,800	50,779	51,366	49,608	51,687	50,191	47,810	46,654	45,042	46,800	45,040	40,705	40,705
Cats & Dogs	156,300	157,500	169,600	170,380	167,800	167,410	167,410	161,360	161,360	159,800	159,800	157,690	157,690	156,940	156,940	159,620
Sheep & Goats	767,366	778,715	766,708	755,166	750,080	739,349	732,896	715,460	701,271	668,976	657,068	652,172	630,996	605,307	586,346	580,191
Rabbits	138,967	136,202	135,733	135,620	128,902	130,047	127,918	124,197	125,567	111,997	102,609	99,916	107,810	103,103	101,365	103,595
Horses	292,873	292,873	294,045	304,282	305,402	307,380	307,229	304,176	305,794	308,231	308,900	308,730	308,973	301,278	297,348	295,601
Other	30,652	30,860	32,184	31,002	31,484	31,308	31,308	30,602	30,293	30,405	30,405	34,972	34,972	34,836	34,836	34,858
Total	17,946,803	18,074,753	18,459,587	17,934,009	17,382,681	17,095,898	16,371,990	16,361,458	16,576,575	16,623,560	16,414,571	16,216,519	16,010,147	15,774,401	15,749,818	15,746,373

B. Guide to indicators

This guide has been developed to offer methodological foundations for facilitating the implementation of monitoring of antimicrobial consumption, and the interpretation and understanding of its results.

The data received by ANSES-ANMV are overall national data that essentially provide a general idea of consumption but also enable comparisons to be made between countries or species, or with human medicine, etc.

Measuring drug consumption involves the use of different sales measurement units. Through the various European national monitoring schemes and different breeding surveys, several indicators of animal exposure to antimicrobials have been developed. All have their own value and limitations.

To adequately reflect the reality of antimicrobial use, it seems important that the monitoring indicators take into account both the exposure to antimicrobials and the population studied: this therefore requires a numerator representing exposure to antimicrobials and a denominator representing the population likely to be exposed.

This guide is not an exhaustive list of the different indicators identified but describes the indicators used for the French national monitoring scheme.

The national sales monitoring scheme enables sales of antimicrobials to be expressed according to two types of measurements:

- sales of antimicrobials can be measured via the weights of active ingredient,
- or exposure to antimicrobials can be measured via an estimate of the body weight treated, the number of animals treated, etc.

1. Numerators

- *A measurement of the quantities of antimicrobials sold: the weight of active ingredient*

The weight of active ingredient sold by drug is an ***exact measurement*** obtained by multiplying the quantitative composition of active ingredient for each presentation by the number of units sold.

The weight of active ingredient sold per species is an estimated amount derived from the weight per drug and the (estimated) breakdown by species provided by the pharmaceutical company.

This way of expressing results is the most direct and most common. However, while this indicator enables changes in sales over time to be monitored, it does not accurately reflect the use of antimicrobials, as differences in dose and treatment duration are not taken into account. It does not enable comparisons to be made between classes of antimicrobials, and comparing total tonnage between years for the same country is complicated by the fact that the breakdown of sales by class changes.

The following example illustrates the calculation of the weight of active ingredient for a drug, and the amount attributed to the target species given the breakdown by species provided by the pharmaceutical company.

Figure B1. Application to an example: calculation of the weight of active ingredient in a calendar year for a given drug available in two presentations

	Presentation 1		Presentation 2
Package size	5 kg		25 kg
Amount of antimicrobials per presentation (kg)	0.5		2.5
Sales for 2012	120		85
Weight of active ingredient (kg)	60		212.5
	272.5		
Breakdown by species	Calves (40%)	Sheep-Goats (20%)	Pigs (40%)
Weight of active ingredient per species (kg)	109	54.5	109

Data available in the drug's Summary of Product
Data provided by the pharmaceutical company
Calculated data

- *A first measurement of animal exposure to antimicrobials: the number of potentially treated kg/day or ADDkg*

This corresponds to an indicator used in human medicine: the number of DDDs.

In human medicine, the DDD (defined daily dose) is a unit defined by the WHO and used for comparisons of drug consumption among different populations. This is a daily reference dosage determined by international experts, which is taken to be the usual dosage for a 70 kg adult in the main indication of an active ingredient.

This indicator was selected by the European Surveillance of Antimicrobial Consumption (ESAC) programme for human medicine.

To calculate the number of DDDs (number of days of treatment at the reference dose), the total amount in grams of the antimicrobial in question must be divided by the value of the DDD in grams for the same antimicrobial.

In veterinary medicine, daily doses have not been defined, as the exercise is more complex than in human medicine because of the variety of species and therefore of daily doses in mg/kg, and the diversity of weights at treatment (as in human medicine, it can be difficult to establish a single treatment weight).

In the context of sales of antimicrobials, ANSES-ANMV has estimated the ADDkg, which corresponds to “the number of kg/day potentially treated” (equivalent to the number of animals treated x weight at time of treatment x number of days of treatment):

Thus, a 50 kg pig treated for 10 days corresponds to 500 ADDkg, and a 65 kg pig treated for 1 day corresponds to 65 ADDkg.

As reference dosages by active ingredient are not determined in veterinary medicine, the ADDkg calculation is based on the daily dosage recommended in the MA. For each drug, for each species, a dosage is chosen to calculate the number of ADDs. When the SPC offers several dosages for a given species, the dosage used corresponds to the highest dosage for ordinary use of the drug.

The amount of body weight treated/day is an **estimated quantity**.

The following example illustrates the calculation of the number of ADDkg for a drug, for the different target species. The daily dose used corresponds to that of the MA for ordinary use of the drug.

Figure B2. Application to an example: calculation of the number of ADDkg in a calendar year for a given drug available in two presentations.

	Presentation 1		Presentation 2
Package size	5 kg		25 kg
Amount of antimicrobials per presentation (kg)	0.5		2.5
Sales for 2012	120		85
Weight of active ingredient (kg)	60		212.5
	272.5		
Breakdown by species	Calves (40%)	Sheep-Goats (20%)	Pigs (40%)
Weight of active ingredient per species (kg)	109	54.5	109
Maximum daily dose (mg/kg)	40	40	50
ADDkg (body weight treated x duration of treatment)	2,725,000	1,362,500	2,180,000

- *A second measurement of animal exposure to antimicrobials: the amount of body weight treated, ACDkg or WAT*

The weight of animals treated with the various antimicrobial classes is obtained by dividing the sales volume expressed in weight of active ingredient by the quantity of active ingredient required to treat one kilogram of body weight (daily dose multiplied by the duration of treatment). The combination of dosage and duration of treatment used is that from the SPC. The weight of animals treated depends on the recommended doses and treatment durations, which may be different from those prescribed in the field.

When the SPC proposes several dosages and durations of treatment for the same species, the dosage and duration used correspond to the highest dosage and duration for ordinary use of the drug.

The body weight treated is an **estimate** of the actual body weight treated. But when the species breakdown provided by the pharmaceutical company corresponds to the field use of the drug by different species and when the dosage used in the field corresponds to the dose and duration specified in the MA, the estimated body weight treated should correspond to the actual body weight treated.

This indicator reflects the use of the different classes of antimicrobials better than the weight of antimicrobials sold because it allows the relative share of body weight treated with each class of antimicrobials to be estimated.

The following example illustrates the calculation of the amount of body weight treated for a drug, for the different target species. The daily dose and duration of treatment used correspond to those of the MA for ordinary use of the drug.

Figure B3. Application to an example: calculation of the amount of body weight treated in a calendar year for a given drug available in two presentations.

	Presentation 1		Presentation 2
Package size	5 kg		25 kg
Amount of antimicrobials per presentation (kg)	0.5		2.5
Sales for 2012	120		85
Weight of active ingredient (kg)	60		212.5
	272.5		
Breakdown by species	Calves (40%)	Sheep-Goats (20%)	Pigs (40%)
Weight of active ingredient per species (kg)	109	54.5	109
Maximum daily dose (mg/kg)	40	40	50
ADDkg (body weight treated x duration of treatment)	2,725,000	1,362,500	2,180,000
Maximum dose for the duration of treatment (mg/kg)	400	400	500
(ACDkg) Body weight treated (in kg)	272,500	136,250	218,000

- *A third measurement of animal exposure to antimicrobials: calculating the number of animals treated*

Once the body weight treated has been estimated, it is easy to calculate the number of animals treated once we have knowledge of the weight of the animals at the time of treatment.

It is not currently easy to collect this information, which is nevertheless essential for assessing antimicrobial therapy practices.

Legislation requires MA holders to provide ANSES-ANMV with regular pharmacovigilance reports: Periodic Safety Update Reports (PSURs). In these reports, MA holders have to estimate the incidence of adverse events and thus calculate the number of animals treated for each species. To do this, they must have a precise idea of the weight at treatment.

In some PSURs, information concerning the weight at treatment is not available. If there has been no reporting of adverse reactions, the incidence is zero and the pharmaceutical company does not transmit any information on the weight at treatment to ANSES-ANMV. In other cases, so as not to underestimate incidence, the companies may use a maximum weight at treatment.

Breeder surveys are the ideal source for obtaining information on weight at treatment. But these are not sufficiently widespread at the moment and cannot provide this information for all drugs and all species.

In the context of harmonised European monitoring, weights at treatment have been defined for the different species by category. So cows and male cattle weigh on average 425 kg at treatment, heifers 200 kg and calves 140 kg. Pigs are on average 65 kg at treatment and sows 240 kg. Kids and lambs are 20 kg at treatment, other sheep and ewes are 75 kg. Chickens are 1 kg at treatment and turkeys 6.5 kg. ANSES-ANMV considers that these set weights, regardless of the class used, are too far from the realities in the field and prefers to use weights derived from field surveys or weights from the PSURs. The weights determined by the EMA are used as a last resort.

The following example illustrates the calculation of the number of animals treated for a drug, for the different target species. Weights at treatment are those from the PSURs.

Figure B4. Application to an example: calculation of the number of animals treated in a calendar year for a given drug available in two presentations.

	Presentation 1		Presentation 2
Package size	5 kg		25 kg
Amount of antimicrobials per presentation (kg)	0.5		2.5
Sales for 2012	120		85
Weight of active ingredient (kg)	60		212.5
	272.5		
Breakdown by species	Calves (40%)	Sheep-Goats (20%)	Pigs (40%)
Weight of active ingredient per species (kg)	109	54.5	109
Maximum daily dose (mg/kg)	40	40	50
ADDkg (body weight treated x duration of treatment)	2,725,000	1,362,500	2,180,000
Maximum dose for the duration of treatment (mg/kg)	400	400	500
(ACDkg) Body weight treated (in kg)	272,500	136,250	218,000
Weight at treatment	70	15	25
Number of animals treated	3,893	9,083	8,720

- *Mean treatment duration*

When sales of antimicrobials are expressed in ADDkg and in ACDkg by class, we can **estimate** a mean treatment duration by class for all routes combined, by dividing sales expressed in ADDkg by those expressed in ACDkg.

2. Denominators and the derived indicators

The denominator should represent the population of users or potential users of antimicrobials. The denominator is intended to reflect population changes over time and does not necessarily correspond to the physical measurement of a biological reality.

- Number of animals
- Mass potentially treated with antimicrobials (kg of product)
- Slaughtered mass (kg slaughtered)
- The ESVAC denominator, the Population Correction Unit (PCU), is obtained by multiplying the number of animals per species category by a set weight that is assumed to correspond to the weight at the time of treatment (425 kg for cows and male cattle, 200 kg for heifers and 140 kg for calves, 65 kg for pigs, 240 kg for sows, 1 kg for chickens, 6.5 kg for turkeys, etc.).

Some indicators

✓ Quantities of active ingredient in mg of active ingredient per kg of product

The denominator mainly used by ANSES-ANMV is the animal mass potentially treated with antimicrobials. When the weight of active ingredient is divided by this denominator, we obtain the sales in milligrams of active ingredient per kilogram of body weight.

✓ ALEA

When the body weight treated is divided by the animal mass potentially treated with antimicrobials, we obtain an expression of sales in Animal Level of Exposure to Antimicrobials (ALEA), the exposure indicator used by ANSES-ANMV.

The ALEA, which is correlated with this percentage of animals treated, is easy to calculate and provides information on animal exposure to antimicrobials.

$$\text{ALEA} = \frac{\text{Live weight treated}}{[\text{Total number of animals}] \text{ x } [\text{Weight of adult animals or at slaughter}]}$$

$$= \frac{\text{Live weight treated}}{\frac{\text{Weight of adult animals or at slaughter}}{\text{Total number of animals}}}$$

- ✓ Percentage of animals treated

The percentage of animals treated would be a good indicator of exposure, but it is difficult to calculate through a national monitoring scheme.

To obtain it, the number of animals treated needs to be divided by the total number of animals. As it is difficult to obtain a good idea of the number of animals treated, this indicator is currently little used in the national monitoring of antimicrobial sales.

$$\text{Percentage of animals treated} = \frac{\text{Number of animals treated}}{\text{Total number of animals}} = \frac{\frac{\text{Live weight treated}}{\text{Weight of animals at treatment}}}{\text{Total number of animals}}$$

$$= \text{ALEA x } \frac{\text{Weight of adult animals or at slaughter}}{\text{Weight of animals at treatment}}$$

Agence nationale de sécurité sanitaire
de l'alimentation, de l'environnement et du travail
14 rue Pierre et Marie Curie
94701 Maisons-Alfort Cedex
www.anses.fr

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