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Antimicrobial Resistance and Animal-Health Awareness Day

**ANSES is taking action to fight
the development of antimicrobial resistance**

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ANSES is taking action to fight the development of antimicrobial resistance

The development of resistance to antimicrobials is a serious concern for human and animal health in Europe and around the world, because it can undermine the effectiveness of antibiotics. In regard to veterinary medicine, antimicrobial resistance is the focus of a Europe-wide strategic plan drawn up by the Heads of Medicines Agencies and instigated during the French presidency of the [Council of the] European Union.

Over the past decade, AFSSA — which was incorporated into ANSES on 1 July 2010 — has been taking action. In 2006, it issued a report entitled “Veterinary Use of Antibiotics, Bacterial Resistance and Consequences to Human Health” whose recommendations are more valid than ever.

To coordinate and enhance the efforts of all those involved, the French Ministries of Agriculture and Health, in close cooperation with ANSES, have decided to set up a National Veterinary Committee to promote a more rational use of antibiotics. This committee is to meet in early 2011 to draw up a plan of action.

In this context, ANSES is marshalling all its resources for conducting studies, research and risk assessments to define — on an unbiased scientific basis — the most appropriate actions to take for a resolutely proactive policy to fight against the selection, emergence and spread of antimicrobial resistance. This policy ties in with the initiatives taken on the European level and, given that the risks involved are global, sets out international recommendations for monitoring and research.

Three priority areas have been developed:

1. Collecting data to better discern the use of antibiotics in various livestock sectors

- Since 1999, the French National Agency for Veterinary Medicinal Products, in collaboration with the French Veterinary Medicine Industry Association (SIMV), has been **monitoring the national sales in France of veterinary medicinal products** containing antibiotics. Analysis of sale results in 2009 shows a decrease in sales of veterinary medicinal products compared to 2008. In addition, fluoroquinolone sales have stabilised whereas cephalosporin sales have decreased.
- Studies on how antimicrobials are used in each livestock production sector and on the prevalence of antimicrobial-resistant bacteria in animals, in food of animal origin and in the environment are conducted by the ANSES Laboratories in Ploufragan, Fougères, Lyon and Maisons-Alfort.

- A survey of pig farmers on the **use of antimicrobials in the pig sector** showed that, in a sample of 83 finishing farms surveyed from 2005 to 2008, the amount of antimicrobials prescribed decreased by approximately 10%. There was high variability among farms, indicating that there is room for improvement.
- Based on data gathered in 2007-2008 by the national network for the surveillance of antimicrobial resistance in pathogenic bacteria of animal origin (RESAPATH), by the 'Salmonella' network as well as by the monitoring programmes involving slaughterhouses, ANSES published the **FARM 3 report** (French Antimicrobial Resistance Monitoring in bacteria of animal origin). This report attests to an alarming increase in *Escherichia coli* that are resistant to cephalosporins, mainly through the production of extended-spectrum beta-lactamases (ESBLs): 2 to 6% of isolated *E. coli* are reported to be resistant in the FARM 3 survey compared to only a few isolations during the FARM 2 survey (2005-2006).

2. Conducting research to better understand the mechanisms involved

- In the poultry sector, ANR-funded research is studying the risks related to the development of **fluoroquinolone-resistant strains of *Campylobacter*** and weighing them against the expected therapeutic benefits [of fluoroquinolones] in treating avian colibacillosis. To estimate the pertinence of regulatory measures that would prohibit these antibiotics in poultry farming, as has been done in some countries such as the United States, the objective of this research is to scientifically evaluate the benefits and drawbacks of using fluoroquinolones in the poultry sector compared to other types of treatment. This project will end in late 2011.
- Early in 2011, ANSES will initiate a research project to evaluate the impact of **treating hatcheries with cephalosporins** — a practice that is occasionally observed — on antimicrobial resistance. Third-generation cephalosporins are very important antibiotics for human health.
- As part of an ANSES call for research proposals in 2011, studies on the **mechanisms behind the transfer of antimicrobial resistance among non-culturable intestinal bacteria** may be developed to better understand the development of antimicrobial resistance in humans through the food chain, particularly *via* products imported from certain regions in the world.

3. Assessing the risks of the use of antimicrobials in veterinary medicine so as to draw up recommendations for public authorities and for those who prescribe them

The use of antimicrobials as growth promoters in livestock production has been banned in Europe since 2003. To go one step further to preserve the effectiveness of antibiotics through more rational use in veterinary medicine, the benefits must be weighed against the risks when defining the treatment strategy: prophylactic, metaphylactic¹ or curative for livestock, and preventive and curative use in pets.

In particular, the assessment will focus on the most sensitive categories of antibiotics: cephalosporins and fluoroquinolones. For these antimicrobial classes, the emergence of generic antibiotics over the past years has led to an increase in their use.

Studies will include human exposure to resistant commensal bacteria, whether exposure be indirect through foods of animal origin (particularly those that are imported), or direct for livestock farmers and pet owners.

In this context, ANSES' expert committees will be preparing the scientific information on which ANSES bases its recommendations to the public authorities and to antibiotic prescribers by the end of 2011.

¹ Metaphylaxis: timely treatment of a group of animals

Progress since the 2006 AFSSA report

“Veterinary use of antimicrobials, bacterial resistance and consequences to human health”

For the most part, the conclusions and the recommendations of this report deal with improving the information tools (data collected on antimicrobial use and on bacterial resistance and how this data is produced, analysed and interpreted). This is essential for setting up a rational plan for controlling antibiotic use in livestock production and for evaluating its consequences on human health.

1. Antimicrobial use

1.a Procedure for marketing veterinary antibiotics

In the medium term, the assessment procedures carried out for applications for marketing authorisation (MA), which follow European-wide, harmonised guidelines, should combine clinical trials with pharmacological and bacteriological data on the relationship between treatment, its efficacy and its impact on selection for antimicrobial resistance.

1.b Improving the monitoring of veterinary antimicrobial use

This is a short-term priority.

The monitoring system for antibiotic use in livestock production has been improved by taking the following actions:

- Since 2007, statements on antimicrobial sales have been compared with pharmaceutical companies' declared turnover for medicinal products. This work was carried out by AFSSA² via the National Agency for Veterinary Medicinal Products (ANMV) in close collaboration with the implicated AFSSA Laboratories and the French Veterinary Medicine Industry Association (SIMV).
- Data continue to be collected with the participation of livestock farmers and other professionals in livestock production sectors. The Ploufragan Laboratory conducted additional surveys in the poultry sector (2008), the swine sector (2009) and the rabbit sector (2010).
- ANSES' Lyon Laboratory conducted surveys on veterinary prescription and use in livestock production for the cattle and sheep sectors in 2007 and surveys are in progress for the goat sector.

1.c Contributing to antibiotic practices and professional training

Various actions have been taken to improve the practices of health professionals:

- Summaries of product characteristics (SPC) for the veterinary medicinal products sold in France continue to be drafted and published on-line (www.anmv.anses.fr); for antimicrobials, the procedure of preparing an 'SPC update' common to all products containing the same active ingredient and with the same pharmaceutical form is now standard.

² On 1 July 2010, AFSSA was incorporated in ANSES following a merger with the French Agency for Environmental and Occupational Health Safety (AFSSET).

- Monthly publication of ANSES ANMV decisions on MA and temporary MAs for veterinary medicinal products (www.anmv.anses.fr).

ANMV requests that the National Committee for Veterinary Medicinal Products, created by Decree no 2010-871 of 26 July 2010 and to be set up by 1 January 2011 at the latest, focus on reviewing antimicrobial treatment regimens. This revision work will naturally be carried out in collaboration with other European agencies that regulate medicinal products.

The French National Association of Veterinary Technical Service Providers (SNGTV) has drawn up a good practices guide and undertaken a review of the [potentially] dangerous practices in various livestock sectors. ANSES is closely involved in this work.

Efforts in vocational training and continuing professional development need to be pursued; in view of this goal, representatives from national veterinary schools will be included in the National Veterinary Committee to promote the rational use of antimicrobials. Likewise, representatives from the various livestock sectors could contribute to educating livestock farmers on this issue.

1.d Information on antimicrobials users

- Publication of data from the monitoring programme on antimicrobial use and bacterial resistance in animals, FARM reports, sales monitoring report, RESAPATH monitoring network report. All of these documents are available on the ANSES website at www.anses.fr.

2. Impact of antibiotic use on resistance in bacteria of animal origin

2.a Monitoring resistance in animals and in food products

In France, information on bacterial resistance to antimicrobials in animals is provided through the following monitoring programmes:

- Monitoring veterinary intestinal bacteria (both sentinel and zoonotic bacteria), implemented by ANSES in collaboration with public and private veterinary laboratories, as part of a monitoring plan set up by the General Directorate for Food (DGAL);
- Monitoring veterinary pathogens, conducted by ANSES in collaboration with volunteer public and private laboratories, as part of a contract with DGAL.
- Monitoring *Salmonella* in various ecosystems, piloted by ANSES with the collaboration of volunteer public and private laboratories;
- Monitoring bacteria of human origin, coordinated by the French Institute for Public Health Surveillance (InVS) and implemented by National Reference Centres;
- Monitoring food products as part of controls in commercial trade.

Monitoring antimicrobial-resistant bacteria in animals is done through collaboration between veterinary services, public and private veterinary testing laboratories, research organisations, and the National Epidemiological Observatory on Antimicrobial Resistance (ONERBA) and through coordination with the European monitoring programme "Antimicrobial resistance in bacteria of animal origin" (ARBAO).

Nonetheless, these networks do not cover all livestock production sectors. Moreover, monitoring resistance rates for bacteria found in food is only regularly reported for *Salmonella* and there is not much information on other bacteria transmitted through food.

Finally, the resistance rates according to bacteria species differ from the rates of prevalence of resistant bacteria in animals or animal products and therefore do not directly reflect consumer exposure to resistant bacteria, nor the public health risk.

It is necessary to transform this monitoring system into a more active system to increase its sensitivity for early detection and to ensure its stability over time. Since 2006, the development of European recommendations and the designation of a European Union Reference Laboratory have underpinned the European monitoring system. This monitoring system led to the first surveys on the prevalence of *Salmonella* in poultry and swine production and of methicillin-resistant *Staphylococcus aureus* in swine production.

2.b Collating data on antimicrobial use with data on resistance

To obtain data on both antimicrobial use and resistance rates, several studies have been carried out in ANSES' Ploufragan/Plouzané Laboratory. These studies have helped identify specific courses of action that can be taken to modify the use of certain antibiotics and adjust current practices.

3. Spread of resistant bacteria to humans and consequences for public health

3.a Estimating and monitoring the human health consequences of antimicrobial resistance in ubiquitous and zoonotic bacteria

This is the major short-term recommendation in the 2006 AFSSA report.

- Develop studies that use a cohort approach or that cross-match different databases:

The public health cost of resistance has not yet been rigorously addressed due to the lack of research conducted by specialised medical research groups. The impact of the cost of resistance in animals on public health is a supplementary research goal.

- Coordinate actions on an early warning system and monitoring of bacterial resistance, on the use of antibiotics and on anticipating the risk arising from bacterial resistance:

ANSES has fully supported the setting-up of a veterinary medicine committee for the rational use of antimicrobials. The human health and animal health sectors need to be coordinated and the close connection between them will be taken into account in the future national plan for rational use of antimicrobials in veterinary medicine to which ANSES will provide scientific and technical support

- Assess gene flow:

The spread of antimicrobial-resistant bacteria from animals to humans is not only possible but there is much evidence to show that certain pathogens have already spread. However, gene flow has been little, or not at all, quantified.

Quantifying gene flow would require very sensitive monitoring tools (as much in animals as in humans) designed to detect the mechanisms of resistance and not just the sensitive phenotypes. It would then be possible to prospectively quantify the emergence rate of a particular type of resistant strain in animals after it had emerged in humans and vice versa.

3.b Mathematical models and quantitative risk analysis

Producing reliable data on human and animal exposure to antimicrobials as well as robust monitoring data on resistance in zoonotic bacteria should lead to the construction of models to quantitatively assess the risks involved.

Consult the “Veterinary use of antibiotics, bacterial resistance and consequence for human health” report on the ANSES web site at www.anses.fr.

Garnering more complete knowledge on farm use and practices

The study of the use of antimicrobials in veterinary medicine in France is based on the combination of two types of investigation, an annual survey of sales of veterinary medicinal products containing antimicrobials and discrete studies in livestock production farms or involving practicing veterinarians.

1. Initial results on the monitoring of veterinary antimicrobial sales in 2009

Since 1999, ANSES has monitored the sales of veterinary antimicrobials every year. Based on OIE guidelines on “Monitoring the quantity of antibiotics used in livestock production”, this monitoring programme is carried out in collaboration with the French Veterinary Medicine Industry Association (SIMV) and with support from the French Ministry of Agriculture.

Why monitor the sales of antimicrobials?

In addition to monitoring bacterial resistance, data on antimicrobial sales are one of the essential elements for assessing the risks related to antimicrobial resistance as well as for proposing measures for risk management and for monitoring practices to evaluate their effectiveness.

How is the monitoring survey carried out?

Monitoring of antimicrobial sales is based on the sales figures provided by the companies that market antimicrobials. These data can be cross-checked with other sources of information (reported annual turnover, prescription surveys, etc.).

The data collected from [pharmaceutical] companies cover 100% of all authorised products. Use of human medicinal products outside the terms of their MA or extemporaneous preparations prescribed under the provisions for making decisions on choice of treatment (article L. 5143-4 of the Public Health Code) are not taken into account. This year, for the first time and for most products, companies reported the sales according to target livestock species. For certain species, the reports could be confirmed by surveys on veterinary prescription and use in livestock production.

How should results be interpreted?

The sales volumes of antimicrobials do not accurately reflect their use. In effect, recently developed antimicrobials are more active and lower amounts are administered. To assess animal exposure to antimicrobials, the dosage regimen and duration of administration as well as the way the animal population responds to the treatment over time must all be taken into account. Thus, a decrease in sale volumes does not necessarily mean that there has been a decrease in use.

What are the main trends?

- Sales volumes

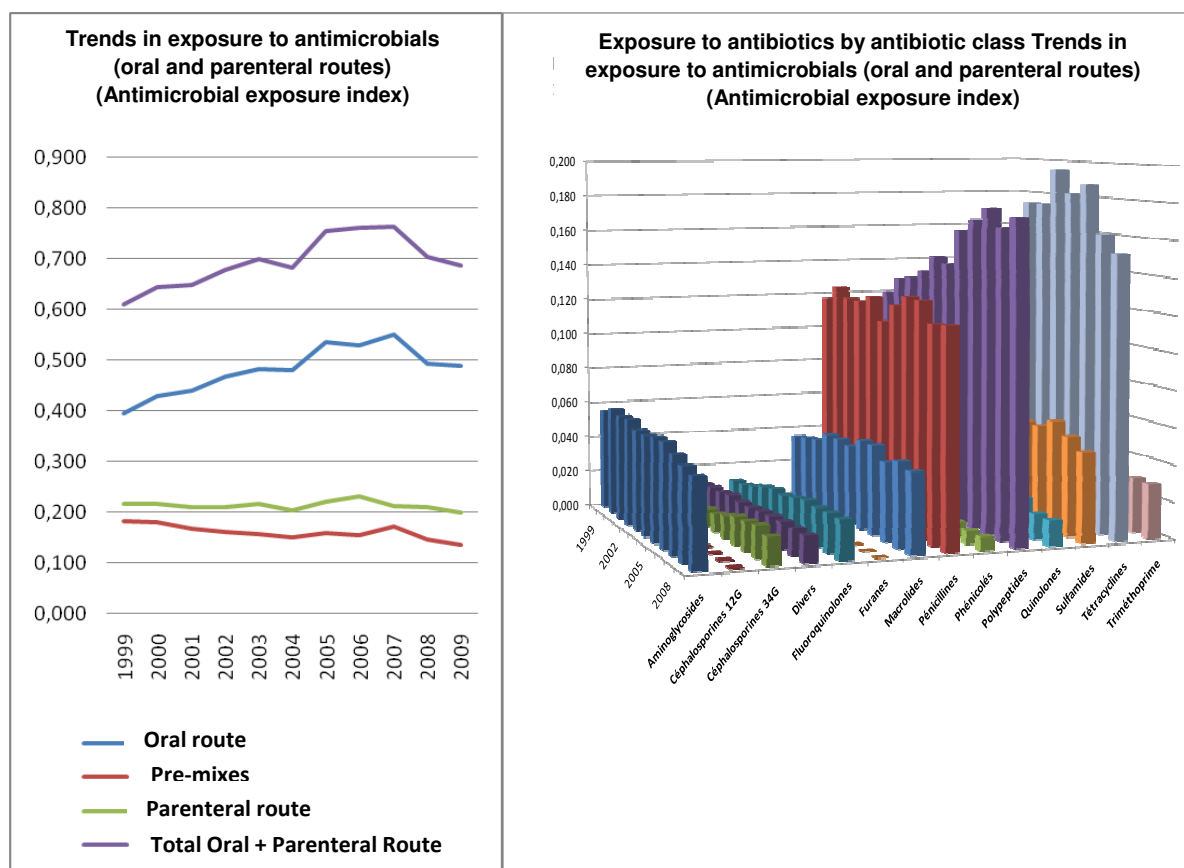
In 2009, the total sales of antimicrobials amount to 1056 tonnes, the lowest volume recorded since the start of the yearly survey.

Compared to 1999, antimicrobial sales have decreased by nearly 20%, this decrease is primarily attributed to two classes of antibiotics, tetracyclines and sulphonamides.

Compared to data obtained in 2008, antimicrobial sales have decreased by 11.3%.

- Animal exposure to antibiotics

From 1999 to 2009, the level of exposure of animals to antimicrobials, all classes combined, given in oral or parenteral administration routes, increased by 12.5%. It decreased slightly from 2008 to 2009 (-2.2%).



Are there trends that justify the implementation of special measures?

Third- and fourth-generation cephalosporins and fluoroquinolones are considered particularly important in human medicine because they are the alternative or one of the only alternatives for treating certain infectious diseases in humans. Therefore, and according to European recommendations, these antibiotics must be reserved for curative second-line treatment.

The overall decrease in antimicrobial sales volumes can be attributed to an increase in the use of more recent and more active antimicrobials.

Thus, compared to 1999, sales of fluoroquinolones have increased by almost 50% and that of cephalosporins have nearly doubled. Likewise, since the beginning of the monitoring survey on antimicrobial sales, the levels of animal exposure to fluoroquinolones has nearly doubled and exposure to cephalosporins has nearly tripled.

Trends in sales and in animal exposure to fluoroquinolones and third- and fourth-generation cephalosporins

| | 1999-2009 trends | | 2008-2009 trends | |
|------------------|------------------|----------|------------------|----------|
| | Sales | Exposure | Sales | Exposure |
| Fluoroquinolones | + 49% | + 93.70% | + 0.09% | + 0.83% |
| Cephalosporins | + 98.4% | + 248% | -13.90% | -15.20% |

Although it seems that from 2008 to 2009 sales and animal exposure to fluoroquinolones did not vary and even decreased for cephalosporins, the strong increase in their use since 1999 is a cause of concern and the downward trends observed in the past two years still has to be confirmed. This is the issue that the national committee for rational use of antibiotic use in veterinary medicine must address in priority.

Where does France stand compared to other European countries?

Today, there are few European countries that monitor antibiotics sales. Nine countries have a more or less developed monitoring system. Moreover, results cannot be easily compared because the type of data collected has not been sufficiently standardised. Monitoring surveys on sales in Europe must be coordinated and this task has just been assigned to EMEA (the European Medicines Agency). France actively participates in developing a coordinated monitoring system and organised a seminar in September 2010 on this topic. Results from a pilot project on a retrospective, harmonised analysis of data collected over the 2005-2009 period are to be published during the first quarter of 2011.

Wherever France stands compared to other European countries, efforts must be undertaken to streamline and reduce antimicrobial use as much as possible. Antimicrobials should only be used in cases where they are absolutely necessary for animal health and welfare.

2. Case study in the pig sector

Conducted by ANSES' Ploufragan/Plouzané Laboratory

Studies in livestock production farms are conducted by ANSES laboratories. They usually focus on one sector and are based on well-delimited datasets (geographic area, study duration). The general objective of these studies is to explore the variability of a given parameter (e.g. prescribed dose) to determine which livestock production factors are associated with variability in use or to compare the properties of different methods for estimating antibiotic consumption.

The 2009 study carried out in farrow-to-finish pig production farms is one such study. This study estimated the quantity of antimicrobials purchased in pig production to explore

- the different ways to quantify antimicrobial purchases using several quantitative indices;
- the variability of these estimates between production farms;
- the changes in antibiotic purchase over intervals of several years

This study, carried out in collaboration with the Brittany Chamber of Agriculture investigated the purchase of medicinal products containing antimicrobials in a sample of 83 farrow-to-finish pig production farms in Brittany. A similar study had been conducted in 2006 on medicinal products purchased in 2005.

Based on the inventory of purchases, the quantity of the corresponding active antibiotic could be calculated.

Given the therapeutic regimen used for the various inventoried antimicrobials and the animals that had been treated (sorted by age class and by farmer), several quantitative use indices were estimated to determine the total quantity of treated biomass³ or the number of animals treated. These parameters were estimated for the whole survey sample as well as by farm and were scaled to the number of kilograms of carcasses produced to standardise the data among farms and sampled batches.

Based on the analysis of the results, purchases were compared by class of antimicrobials, pharmaceutical form, recipient animal age class, farms as well as by calculated index. Data obtained in 2005 were also compared with those of the 2009 study.

Results

Comparing results from 2008 with those of 2005 shows a decrease of roughly 10% in the amount of antibiotics purchased, for all pharmaceutical forms. This decrease is the most pronounced in the age class corresponding to finishing pigs.

In 2008, the oral route (especially through feed) was the main administration route for antimicrobials. Post-weaning piglets are the age class that receives the greatest share of purchased antimicrobials (60 to 70% according to the index used).

Polypeptides, tetracyclines, macrolides, sulphonamides, and beta-lactamines are the main

³ Cumulative weight of animals to be treated

classes of antimicrobials purchased. However, the use of these antimicrobial classes varies with the age of the pigs under consideration.

High variability in purchases was observed among farms. Purchases are dissimilar, with many farms making few purchases and few farms with high purchases.

The upper third of farms represents about 50% of all the antimicrobials purchased in the survey sample.

Among the specific pig production characteristics that could be recorded during the study, very few were statistically correlated with the quantities of antibiotics used. Among these characteristics, animals of different age classes can be considered as a potential risk factor.

Perspectives

Exploration of the reasons behind use and user practices will require supplementary data, involving practicing veterinarians and farmers, to precisely identify the reasons for use and the practical conditions under which antimicrobials are prescribed and administered. These data will make it possible to compare the parameters used in the study to quantitatively estimate antimicrobial consumption with the actual situation.

The variability in consumption (qualitative and quantitative) observed among farms is an essential factor, a key for encouraging less antimicrobial use in farms that purchase high quantities of antimicrobials by emulating farms that purchase smaller amounts. This variability suggests that there are factors (potentially related to [animal] health status, livestock production practices, etc.) that determine antibiotic use. The precise identification of these factors, including sociological parameters, which could be potential driving forces behind a strategy for reducing use of antimicrobials, may require further study. The efforts that can be geared to reducing antibiotic use, whether they be general or specific (to a particular class or practice), should be monitored closely to identify, other than their impact on use, the possible obstacles (health, technical or human) that can prevent reduction.

Monitoring resistance in bacteria

By providing data on the trends and the emergence of resistance in bacteria of animal origin, monitoring is a useful decision-making tool for veterinarians to help them make rational antimicrobial prescriptions and an information tool for managers. Over the past 10 years, ANSES has greatly enhanced its monitoring system and has very actively helped set up a European monitoring scheme.

On the European level, the Zoonoses directive⁴ recommends, in effect, monitoring antimicrobial resistance in *Salmonella* and *Campylobacter* as well as in indicator bacteria species⁵. EFSA drew up technical recommendations for this monitoring scheme and moreover, a network of European and national reference laboratories, coordinated by ANSES' Fougères Laboratory as the EU Reference Laboratory, is working on standardising the techniques and improving the quality of these analyses.

ANSES' work in monitoring bacterial resistance is based on the activities undertaken in several complementary systems and in field studies.

- [RESAPATH](#)⁶ collects data on antimicrobial resistance in bacteria isolated from sick animals as part of the veterinary diagnosis procedure.

- The [Salmonella](#) network⁷ collects *Salmonella* strains of non-human origin (isolated from food, the environment or livestock production) for serotyping and antibiograms

- Annual monitoring plans implemented by the Directorate General for Food (DGAL), in collaboration with ANSES laboratories, involving the collection of faeces or caeca from healthy animals at the slaughterhouse, from which sentinel⁸ or zoonotic⁹ bacterial strains are isolated for the cow, pig and poultry sectors.

Based on these monitoring programmes, ANSES publishes a FARM report every two years to summarise these data.

1. Presentation of the FARM 3 (2007-2008) report

The FARM 3 report presents the results from the monitoring programme on the use of veterinary antimicrobial medicinal products and the percentage of resistance of bacteria isolated from animals in the various programmes for the 2007-2008 period. It is published in

⁴ Directive 2003/99/CE of the European Parliament and of the Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents

⁵ *E. coli*, *Enterococcus faecium*

⁶ Coordinated by the [Lyon](#) and [Ploufragan](#) Laboratories

⁷ Coordinated by the [Maisons-Alfort Food Safety Laboratory](#)

⁸ *E. coli*, *Enterococcus faecium*

⁹ *Campylobacter* spp, and some *Salmonella* isolates

¹⁰ French Antimicrobial Resistance Monitoring in bacteria of animal origin

French and in English so that information can be shared among scientists and veterinarians on both European and international levels.

Main results

- *Salmonella*

Data from ANSES' various monitoring programmes reveal a low level of quinolone-resistant *Salmonella* strains for bacteria isolated from the poultry sector and a few strains resistant to cephalosporins in this same sector. Resistance to these two classes of antimicrobials is rare for strains isolated from other livestock production sectors.

The percentages of resistance vary substantially between *Salmonella* serovars, ranging from "very sensitive to antimicrobials" for the serovar Enteritidis to multidrug resistant serovars such as Typhimurium or Hadar.

The European survey conducted on pig production detected little resistance except to tetracyclines.

- *Staphylococcus*

The survey determined that the prevalence of methicillin-resistant *Staphylococcus aureus* is less than 3% in French livestock production farms, much lower than the prevalence rates reported in the European Union where several member states (Germany, Spain) show rates higher than 40%. Differences between Member States are attributed in part to the way livestock production is structured. In France, production farms are generally small-scale, family-run farrow-to-finish units with little circulation of animals between farms whereas in Germany and Spain, animal transport is frequent with animals from different farms being grouped after weaning.

- *Campylobacter*

For *Campylobacter* strains, the FARM report provides data on the turkey sector for the first time. Strains from turkey production have antimicrobial-resistance percentages comparable to those in the pig and broiler chicken sectors. One particularity is the demonstration of a small percentage of resistance to gentamicin.

- *Escherichia coli*

As part of monitoring programmes in slaughterhouses, data from the 2007-2008 period show that a high proportion of *E. coli* strains have lowered sensitivity to fluoroquinolones in poultry production (turkey and broiler chickens) and in calves. The percentage of resistance is low in the pig sector. This monitoring programme also confirms the presence of *E. coli* strains resistant to cephalosporins (cefotaxime) in poultry and pig production with a percentage of the order of 3%, confirming the emergence revealed in the previous report. This emergence is of special concern due to the importance of this class of antimicrobials in human and veterinary medicine.

The data from the 'RESAPATH' network in charge of monitoring antimicrobial resistance in pathogenic bacteria of animal origin anticipate the data from the other monitoring programmes and show a decrease in cephalosporin sensitivity in pathogenic *E. coli* strains

from poultry and a decrease in sensitivity to quinolones. Similar trends have been observed in pathogenic *E. coli* strains from pigs and calves.

- *Enterococcus*

For *Enterococcus* strains isolated from various sectors, the percentages of resistance are high for erythromycin, tetracycline, clindamycin and streptomycin and low or nil for other antimicrobials, with a low number of isolates resistant to vancomycin and ampicillin.

Conclusion

The data presented indicate that the steady increase in cephalosporin and fluoroquinolone use in livestock production over the past decade has resulted in an increase in the percentages of resistance to these antimicrobials in *E. coli* strains, whether they be commensal or pathogenic in animals. In *Enterococcus faecium*, the FARM data also show a decrease in the percentages of resistance to antibiotic classes exclusively used as growth factors.

2. An example of monitoring of two pathogenic bacterial species: MRSA and *E. coli*

Examples in the poultry and pig sectors

Meticillin-resistant *Staphylococcus aureus* (MRSA) is well-known in human medicine because it currently accounts for roughly half the cases of *S. aureus* isolated from nosocomial infections in France. MRSA is resistant to all the antimicrobials in the beta-lactam class, and some strains show an associated resistance to other classes of antimicrobials (multi-drug resistance). While MRSA has been described in many animal species, the pig is the subject of most studies for two main reasons: in some countries, there is a high prevalence of animals or farms harbouring a specific clone (MRSA ST398) and this clone is associated with a human transmission risk through direct contact with infected pigs. Very few cases of human MRSA ST398 infection have been described to date.

In France, ANSES (Ploufragan and the Food Safety Laboratory in Maisons-Alfort) has carried out three ¹¹ studies in collaboration with DGAL, the Bichat-Claude Bernard University Hospital and the National Reference Centre for *Staphylococcus*, to assess the MRSA reservoir in pigs. One of these studies, funded by the European Commission, is part of a wider survey that aims to establish a European map of MRSA prevalence in pig production farms.

The overall results show that the pig MRSA reservoir in France is low in pig production farms but high in slaughterhouses. Other studies have been undertaken to better understand how this MRSA reservoir gets established in pigs.

¹¹ Jouy et al., RICAI 2008 Conference, <http://www.ricai.org/> et <http://www.efsa.europa.eu/fr/scdocs/scdoc/1597.htm>

Escherichia coli is both a common commensal bacterium ¹² in the digestive tract and, according to its virulence factors and the health of its host, a very pathogenic bacterium for both humans and animals. Its resistance to antimicrobials is thus carefully monitored. In veterinary medicine, owing to the participation of testing laboratories in the RESAPATH network coordinated by ANSES (Lyon and Ploufragan), the first *E. coli* strains resistant to third- and fourth-generation cephalosporins isolated from animal infections were detected in France in 2004. These *E. coli* produce plasmid-mediated CTX-M extended-spectrum beta-lactamase (ESBL), as had already been identified in human medicine.

This resistance is crossed with most other beta-lactams available for humans and all of those that are available for animals. Since they have been detected, the proportion of *E. coli* strains insensitive to third- and fourth-generation cephalosporins (intermediate and resistant strains), isolated from animal infections, has increased. The level of resistant strains remained stable from 2008 to 2009, reaching 1.4% (n=10/10/712) in turkeys and 4.7% (n=63/1356) in pigs. During the same period, the percentage of resistance continued to increase in chickens (both layers and broilers), reaching 12.2% in 2009 (RESAPATH data).

The number of isolations of *E. coli* resistant to third- and fourth-generation cephalosporins has also increased in other countries. The RESAPATH data for 2010 will help assess whether resistance is still increasing or if the observed increase was only due to a discrete event related, for example, to an increase in *E. coli* infections in the poultry sector. In effect, RESAPATH data are based on bacteria isolated in a context (animal infections) that particularly selects for the analysed bacterial strains. The quantification of the reservoir of this resistance in *Gallus gallus* requires confronting RESAPATH data with data from slaughterhouse monitoring programmes as well as the implementation of studies (currently being developed) focusing specifically on *E. coli* resistant to third- and fourth-generation cephalosporins.

The rapid evolution of antimicrobial resistance is of particular concern because it follows a pattern similar to the resistance described in human medicine and risks constituting a reservoir of resistance genes. In veterinary medicine, this resistance decreases the effectiveness of a very important class of antimicrobials that are a last-resort treatment for animal infections caused by multi-drug resistant bacteria.

¹² Commensal bacteria are found on the surface of skin or the mucus membranes of their host (humans or animals) where they live without causing any harm.

Factors in the development of antimicrobial resistance:

Applied research areas at ANSES

The fight to preserve the effectiveness of antimicrobials requires specific research efforts, as underlined by the National Plan for preserving the effectiveness of antimicrobials 2007-2010, piloted by the Directorate General for Health (DGS).

The mechanisms behind the selection of antimicrobial resistance in bacterial populations—either commensal or pathogenic, the emergence of a new mechanism of resistance, and the spread of resistance genes or bacteria are still poorly understood. However, the analysis of the consequences of exposure of human and animal populations to antimicrobial medicinal products on bacterial resistance to antimicrobials is absolutely essential for efficient risk management.

The human health and animal health scientific communities are both currently defining their specific research needs. The issue concerns both human and animal health because there are no barriers between bacterial populations of environmental¹³, human and animal origin in that they can all freely exchange DNA, a natural process that is part of the evolutionary mechanisms of all living organisms.

Along with their referral role for the Ministry of Agriculture, **ANSES Laboratories conduct research on antimicrobial resistance** as part of their monitoring activities. Four laboratories have been actively working on this topic for many years: Fougères, Ploufragan, Lyon and Maisons-Alfort. Their studies are conducted individually or in partnership with other organisations (Institut Pasteur, INSERM, INRA, CEMAGREF, National Veterinary Schools). In addition, the National Agency for Veterinary Medicinal Products is monitoring the sales of antimicrobials for veterinary medicine.

Priority research areas for animal health and public health at ANSES:

Area 1: enhance research on descriptive epidemiology of bacterial zoonoses and on the evolution of sensitivity/resistance to antimicrobials of their bacterial agents.

As part of their mission in epidemiological surveillance, some laboratories study the **prevalence of antimicrobial resistance** in certain specific zoonotic or pathogenic bacteria. They can thereby detect the emergence of antimicrobial-resistant strains in animals, in food and in the environment. In relation to this mission, some research groups are working on characterising **resistance genes** and the interactions between the mechanisms of resistance and metabolic activity in bacteria.

Area 2: analyse the specificities of antibiotic use in animals:

¹³ Main natural source of plasmid-mediated resistance genes that circulate among pathogenic bacteria

- Analysing antimicrobial sales in veterinary medicine to quantify antimicrobial use in the different sectors. ANMV conducts this research in close collaboration with the epidemiology groups at Ploufragan and Lyon.
- Characterising the use of antimicrobials in rural veterinary medicine in each sector according to treatment strategy: prophylaxis, early treatment, and conventional curative treatment. The Lyon and Ploufragan Laboratories conduct pharmaco-epidemiological studies ranging from multiannual monitoring of antimicrobial use in various livestock sectors (pig, poultry, ruminants) to the analysis of prescription and sale practices for antimicrobials with veterinary purposes
- Characterising the use of antibiotics in cat and dog veterinary medicine.

Area 3: study the impact of antimicrobial use on bacterial resistance, particularly in intestinal flora

- Impact of antimicrobial use on emergence and persistence of bacterial resistance in animals

Epidemiological studies on poultry include (1) defining the association between carriage of resistant bacteria to the slaughterhouse and exposure of the sampled animals during their lifetime, and (2) determining the lapse of time between changes in use and their repercussions on resistance through a joint study using two chronological series, one on use practices and the other on resistance.

Pharmacological and bacteriological studies in chickens include (1) the evaluation of the risks/benefits of using fluoroquinolones and (2) the biological cost of resistance to antimicrobials in *Campylobacter*. Other studies address these issues in ruminants (*E. coli* and beta-lactams; *Campylobacter* and fluoroquinolones) or in pigs (study of the conditions favouring selection in intestines during treatment, mathematical modelling of emergence and spread of resistant bacteria in livestock farms).

Early 2011, ANSES will initiate a research project to assess the impact of third-generation cephalosporin treatment practices in hatcheries and on poultry intestinal flora.

- Increase in the risk of transmission of antimicrobial resistance in human populations treated with antimicrobials

This issue is addressed by the Fougères Laboratory in collaboration with INRA/ENV in Toulouse based on a rodent model (simulating both animal and human biology). Using this model, the effects of exposure to antimicrobial treatments (or residues thereof) can be studied on

- flora in the intestinal barrier and risk of implantation of a resistant pathogenic bacterium.
- risk of transmitting plasmid-mediated resistance genes to disrupted intestinal flora bacteria using a simplified model.

Area 4: *study the spread of bacterial resistance from animals to humans through direct¹⁴ or indirect¹⁵ exposure*

In particular, through the ANR project “Assessment of the use of fluoroquinolones in poultry”, the Ploufragan and Fougères Laboratories have initiated research with multiple partners on the spread of antimicrobial resistance in the environment: Study of the persistence or selection for bacteria resistant to fluoroquinolones in manure, or soil and water after manuring and study of gene transfer to soil bacteria.

These four research areas form the basis for the future development of quantitative risk analysis and for guiding risk management. The needs for research in the fight against the development of antimicrobial resistance are great and ANSES will contribute to defining them by animal sector as part of a future plan for the rational use of antimicrobials in veterinary medicine.

¹⁴ At the workplace for livestock farmers, at home for pet owners

¹⁵ via food of animal origin, or via the environment (soil and water) polluted by effluents from livestock production or the food-processing industry

Animal health and welfare at ANSES

More than 30% of its research groups are devoted to animal health and well-being

On 1 July 2010, AFSSA and AFSSET merged to become ANSES, the National Agency for Food, Environmental and Occupational Health & Safety. This new public health agency carries on the missions and has inherited the means and personnel of both its former agencies. It also capitalises on the achievements and the values inherited from AFSSA and AFSSET, including scientific know-how, unbiased risk assessment and a wide range of expertise, for a more comprehensive and cross-cutting perspective on public health issues

ANSES' main mission is to contribute to the protection of human health with respect to the environment, the workplace and food, but also to contribute to the protection of animal and plant health. Given its extensive expertise, ANSES will be able to identify all the risks to which humans are exposed, intentionally or not, at all ages and times of life, at work, at home, while travelling or as part of leisure activities.

By striving to improve animal health, ANSES helps reinforce public health measures and food safety, monitors the emerging risks for humans and helps ensure secure food supplies and good economic health for the agri-food industry.

ANSES contributes to preventing and controlling dominant and emerging animal diseases that affect livestock or wild animals (echinococcosis, avian flu, tuberculosis, PWD, etc.) that are:

- transmissible to humans either directly (e.g. rabies or Q fever) or through food (BSE, listeriosis, salmonellosis, etc.);
- specific to animals (foot-and-mouth disease, swine cholera, bluetongue or certain livestock diseases with a high economic impact such as piglet wasting disease, PWD).

Through its research and its expertise, ANSES participates in protecting animals and their welfare.

Better understanding animal diseases

ANSES studies pathogenic agents:

- it analyses the causes of onset and spread of disease within livestock farms, from a wild animal reservoir or due to livestock production and feed practices;
- it assess the risks that arise due to animal diseases, for production sectors and for public health.

Better control of animal diseases

ANSES

- develops diagnostic tools;
- monitors the onset and spread of diseases;
- develops preventive means such as vaccines and seeks alternative treatment methods by improving on the risk factors that are often linked to how livestock are raised and bred;
- controls and assesses the quality and effectiveness of veterinary medicinal products, antimicrobials in particular, and studies their safety for animals, humans and the environment.

Key figures

- **8** laboratories specialised in a livestock sector conduct research. Reference laboratories for several diseases, they provide scientific and technical support to national, European and international authorities.
- Several scientific panels, representing some **100** scientists from various disciplines assess the risks related to animal disease and to veterinary medicinal products.
- **1** reference laboratory for residues of veterinary medicinal products participates in monitoring appropriate use of veterinary medicinal products and antimicrobial resistance.
- **1** national agency for veterinary medicinal products, a health policy authority that controls, authorises and assesses veterinary medicinal products and contributes to the elaboration of many regulatory and technical documents.
- Coordinator or active participant in some **20** epidemiological surveillance networks.

National Agency for Veterinary Medicinal Products: **a health policy enforcement authority**

ANSES is responsible for ensuring the implementation of regulations regarding veterinary medicinal products in the areas for which it is designated in the Public Health Code. ANSES is thus endowed with the power to carry out scientific assessments, inspections and decisions.

It exercises this particular authority through the National Agency for Veterinary Medicinal Products (ANMV).

Active in several international authoritative bodies, ANSES participates in discussions involving veterinary pharmaceuticals.

and contributes to elaborating many regulatory and technical documents in this field. In particular, ANSES is also the collaborating centre for the World Organisation for Animal Health (OIE), participates in work of the United Nations Food and Agriculture Organisation (FAO) and in the World Health Organisation (WHO).

Finally, ANSES is also member of the European Heads of Medicines Agency network.

ANMV assesses

- national and European dossiers for market authorisation of veterinary medicinal products;
- European dossiers on the maximum acceptable levels of residues from veterinary medicinal products in food of animal origin.

Authorises

- the marketing of medicinal products;
- their clinical trials;
- establishment of pharmaceutical companies for the commercialisation, manufacture, wholesale distribution, import and export of veterinary medicinal products:
 - import of veterinary medicinal products;
 - temporary use of medicinal products authorised elsewhere in Europe or in other countries.

Monitors

- the risk of undesirable effects of medicinal products.
- the quality of medicinal products.
- the operation of veterinary pharmaceutical companies.
- advertising for veterinary medicinal products.
- import and export of veterinary medicinal products.

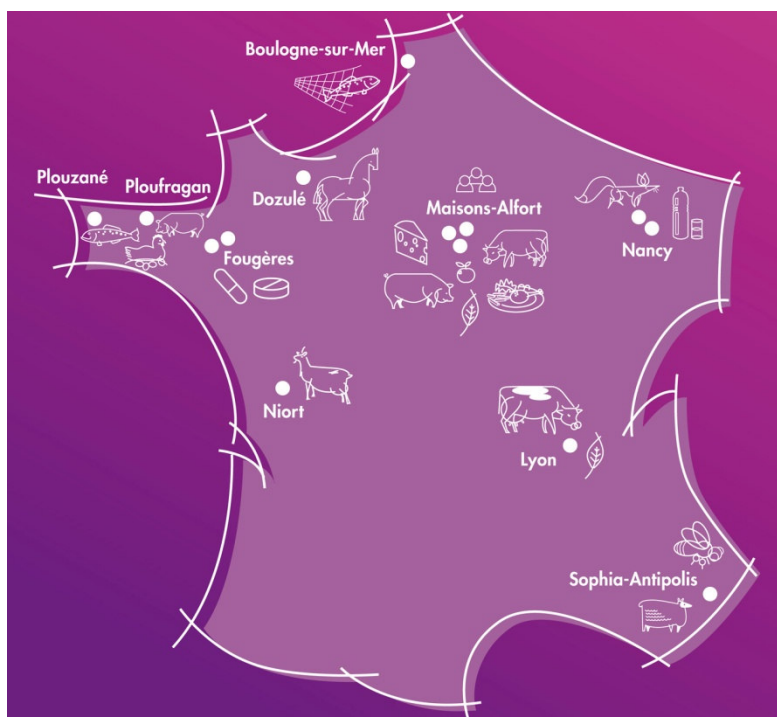
Veterinary pharmacovigilance consists in monitoring the risk of adverse reactions caused by veterinary medicinal products. ANMV gathers data on:

- the effectiveness of medicinal products;
- the consequences of medical treatment in terms of residues in food of animal origin (validity of withdrawal periods);
- their impact on the environment.

It also studies non-compliant use that disregards the labelling and safety information of veterinary medicinal products.

* Minimum lapse of time between the administration of a medicine and marketing of animal-based food products.

ANSES Laboratories



The ANSES Laboratories that study antimicrobial resistance:

- Fougères

The Fougères Laboratory — with a staff of 65 — contributes chiefly to a better understanding of:

- the benefits and the risks associated with the use of veterinary medicinal products and disinfectants in the agri-food industry;
- the risks associated with food contaminants.

Its work focuses on:

- screening for residues of veterinary medicinal products in food of animal origin;
- the antimicrobial efficacy of antibiotics and disinfectants and resistance to these products;
- assessment of genotoxicity of food contaminants.

Reference Laboratory for residues from veterinary medicinal products and resistance to antimicrobials, it participates in monitoring and controlling these health risks. Participant in the standardisation of methods for determining the effectiveness of disinfectants, it also contributes to the assessment of European biocidal products. Data from these investigations are useful for the proper use of veterinary medicinal products and antimicrobial hygiene products in France and in Europe.

Through its research in toxicology, it also provides the data necessary for assessing the risks of contaminants and residues in food.

- Lyon

More than 75 people work at the Lyon Laboratory that is committed primarily to improving ruminant health. It is specialised in transmissible spongiform encephalopathies, antimicrobial resistance, mycoplasmosis and some viral diseases (Rift Valley fever):

- it studies the pathogenic agents that cause major and emergent diseases
- it studies pathogenic bacteria in ruminants (antimicrobial resistance and virulence)
- it monitors the onset and spread of diseases and analyses their causes
- As the National Reference Laboratory for several diseases, it provides scientific and technical expertise for the veterinary controls carried out by public authorities (validation of data and analysis methods, training for field laboratories, management of epidemiological surveillance data, etc.).

The Lyon Laboratory also has a unit dedicated to monitoring and studying the processes behind resistance of plant pests to phytosanitary products.

- Maisons-Alfort - Food Safety Laboratory

This 150-person strong laboratory works on the biological and physico-chemical hazards that can affect food safety.

In this capacity, it participates in the activities of reference, research, monitoring, epidemiology and scientific and technical expertise for ANSES.

The Maisons-Alfort Laboratory brings scientific expertise to public decision-making processes, both on general food safety issues and also on issues that are specific to certain agri-food sectors (milk and dairy products in particular).

It also identifies, monitors and analyses the risks of the main threats to food safety:

- microbiological hazards related to raw materials, food processing and preparation;
- the physico-chemical hazards present in the environment or generated by agri-food industry procedures and that can be found in food.

It also determines antibiograms (COFRAC accreditation) and the minimum inhibitory concentrations for *Salmonella* and *Staphylococcus* strains.

These data are used in the Salmonella network and the DGAL monitoring programmes. They are regularly reported through newsletters and reports issued by the Salmonella network, in FARM reports or in epidemiological bulletins issued by ANSES, in conjunction DGAL and DGS.

- Ploufragan-Plouzané

Spread over its two campuses in Brittany, this laboratory employs 200 people. It is specialised in poultry, pigs and farmed fish species. It works to improve animal health and welfare as well as the safety of food of animal origin.

Its main research programmes include:

- adapting statistical methods for epidemiology
- antimicrobial resistance and pharmaco-epidemiology
- poultry and pig welfare
- calicivirus in rabbits and hares
- *Campylobacter*, *Salmonella*, *Listeria*, *Yersinia*
- immunology and immunotoxicology of fish
- impact of environmental pollutants on animals
- avian flu, Gumboro disease and avian metapneumovirus infections
- influenza/flu syndromes in pigs
- interaction between digestive flora and pathogenic bacteria
- host/pathogen Interactions
- modelling infection processes
- enzootic respiratory disease in pigs
- poultry parasitology
- viral diseases in fish
- pig cholera
- vaccinology/vectorology
- emerging diseases

Annex:

ANSES publications that address antimicrobial resistance

Publications that address antimicrobial resistance

2006 to 2010

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