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MONITORING OF ANTIBIOTIC RESISTANCE IN ANIMAL HEALTH AND THE ENVIRONMENT

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Introduction

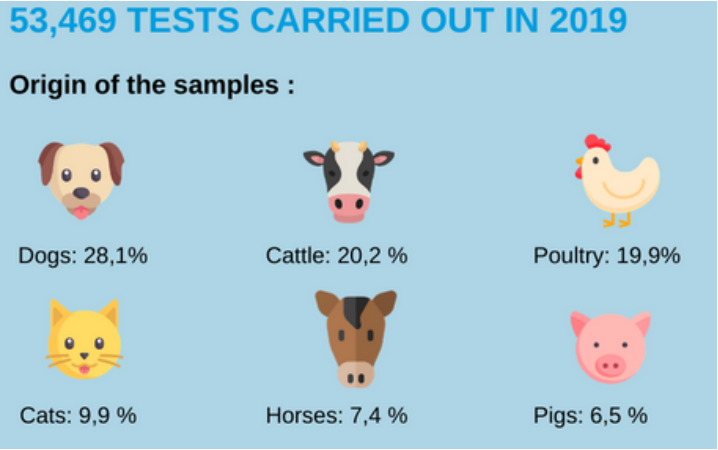
To coincide with European Antibiotic Awareness Day on 18 November 2020, ANSES is publishing the conclusions of several of its studies aimed at preventing the emergence and spread of antimicrobial-resistant bacteria. As it does every year, the Agency is reporting the results of its surveillance of antimicrobial-resistant bacteria in animals and monitoring of sales of veterinary antimicrobials. ANSES is the National Reference Laboratory for antimicrobial resistance, and as such it is also responsible for monitoring bacterial resistance in the food chain as part of national and European efforts to tackle this issue. Besides this regular monitoring, an expert appraisal was conducted this year for the first time to review knowledge of the level of environmental contamination in France by antibiotics, resistant bacteria and the genes conferring this resistance.

What is antimicrobial resistance?

The extensive use of antibiotics over the past few decades has led to the selection of micro-organisms with genes giving them the ability to resist these drugs. These bacteria pose a significant threat to both animal and human health. Indeed, antibiotics effective against pathogenic bacteria are diminishing in number, and for certain multidrug-resistant strains are even non-existent. Antimicrobial resistance is a major public health issue requiring a comprehensive approach. Particular attention is now being paid to resistance to so-called "critical" antibiotics, which are mainly used as a last resort in human medicine when the first antibiotics prescribed have failed to cure a patient.

1 Resapath's observations: the decline in antimicrobial resistance continues

Since 2001, the French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin (Resapath) has monitored the spread of bacteria that are resistant to antibiotics, including those of critical importance to humans, in populations of sick farm animals and pets. A network of 71 veterinary testing laboratories is tasked with detecting these bacteria. During 2019, they carried out 53,469 tests. Escherichia coli was the main bacterial species identified and is the primary indicator for monitoring trends in antimicrobial resistance.



Origin of the samples from the Resapath monitoring

Third- and fourth-generation cephalosporins and fluoroquinolones

Resistance to these two classes of antibiotics is monitored very closely as these are crucial for human health and have few or no alternatives. For these two classes, the proportion of resistant bacteria is **low** and the **downward trend** observed in recent years is continuing: levels of cephalosporin-resistant bacteria range from 1% in pigs and poultry to 4% in cats. Proportions of fluoroquinolone-resistant bacteria range from 3% for pigs, turkeys and horses to 8% for cattle.

There has been a decrease or stabilisation in the levels of resistant bacteria.

Colistin

Colistin is another antibiotic that is closely monitored. Resistance to this antibiotic has been under control for the last 15 years and concerns fewer and fewer strains of bacteria.

Other antibiotics

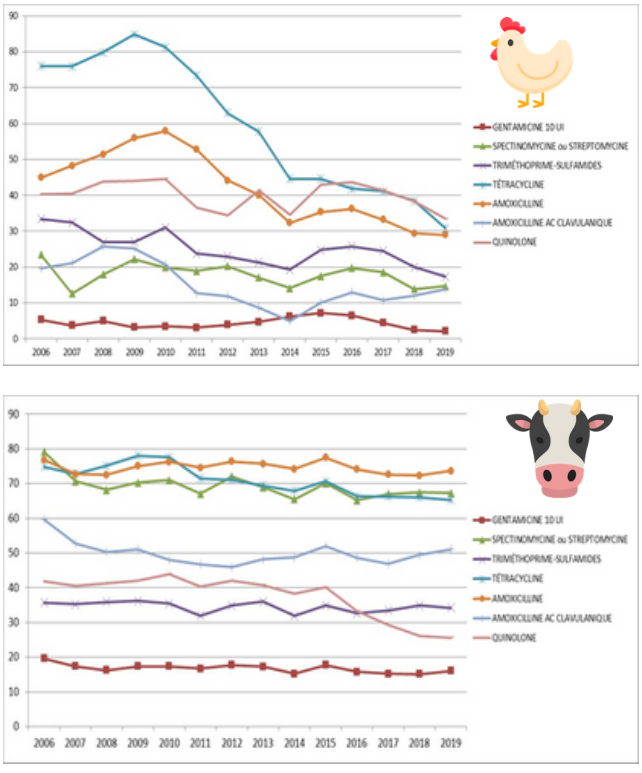
The general trend is a slight decrease or stabilisation in resistance. The situation varies according to the sector: poultry, for which a very sharp decrease in antimicrobial resistance had been observed before 2014, have the lowest levels of antimicrobial-resistant bacteria: this level is no higher than 30% in hens and chickens for the antibiotics responsible for the most resistance, and it is a maximum of 40% for turkeys. The fall in antimicrobial resistance has been less pronounced in pigs and the situation is stable for cattle: the highest levels of resistant bacteria are 65% in pigs and 75% in cattle.

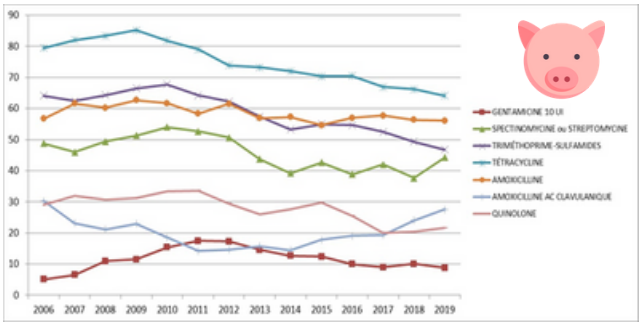
Methicillin resistance

Another major indicator of antimicrobial resistance, methicillin resistance mainly concerned the bacterium *Staphylococcus pseudintermedius*, a staphylococcus species responsible for disease in domestic carnivores. This resistance was present in 15-20% of the strains tested, a phenomenon comparable to that observed in humans for Staphylococcus aureus. Note that *S. pseudintermedius* only very rarely affects humans.

Multidrug-resistant bacteria

These are bacteria that are non-susceptible to more than three antibiotics. They are declining in all sectors combined. In 2019, the proportion of multidrug-resistant strains was highest in cattle, with 15.5% multidrug-resistant bacteria, and lowest in turkeys (2%).





Trends in the rate of antibiotic-resistant bacteria in hens and chickens, cattle and pigs

Read the Respath 2019 annual report in French

2 Monitoring of the use of veterinary medicinal products: animals generally less exposed to antibiotics

Through the French Agency for Veterinary Medicinal Products (ANSES-ANMV), ANSES monitors sales of veterinary antibiotics and animal exposure to them. It does this based on sales of veterinary medicinal products reported by the marketing authorisation holders. The quantity of antibiotics sold is steadily decreasing, with 422 tonnes of antibiotics sold in 2019, **10.5% less than in 2018.** However, the tonnage of antibiotics sold does not reflect actual exposure of animals to antibiotics, as this dépends on the dosage of the drug, the duration of administration and changes in the populations of the different animal species considered. The Agency took into account the recommendations for use of the drugs studied and the estimated weights of the animal populations, to determine the level of exposure of animals to antibiotics.

Main results of the monitoring of sales of veterinary medicinal products for 2019

- The **exposure level was the lowest since monitoring began in 1999**. Compared to 2011, the reference year of the first EcoAntibio plan, which aimed to reduce antibiotic use by 25% in five years, exposure to antibiotics for all animal species combined has fallen by 45.3%.
- This decrease continued in 2019, with an overall reduction of 10.9% compared to the previous year.

- This trend varied according to species: exposure has **decreased in cattle, pigs and poultry**, which have seen falls of 9.9%, 16.4% and 12.8% respectively in one year

- A slight **rebound** was observed in 2019 for rabbits and domestic carnivores (dogs and cats): +1.5% for rabbits and +2.1% for carnivores. This uptick should not overshadow the downward trend observed since 2011.

- Exposure of animals to **critically important antibiotics has fallen sharply** since 2013, and has stabilised in the last three years: between 2013 and 2019, it decreased by 86% for fluoroquinolones and by 94.1% for newer-generation cephalosporins.

- **Colistin**, for which transferable resistance mechanisms have been reported, has seen its exposure rate **fall by 64.2%** from the reference average level between 2014 and 2015. The target of a 50% reduction in five years set by the second EcoAntibio plan for 2017 has been achieved for the pig, poultry and cattle sectors.

Read the ANSES ANNUAL REPORT : Sales survey of veterinary medicinal products containing antimicrobials in France in 2019 (in French)

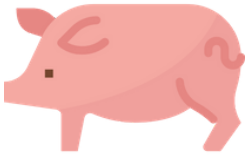
3 European monitoring of antimicrobial resistance

The monitoring of antimicrobial resistance in certain "sentinel" bacteria or bacteria posing a risk of transfer from animals to humans is regulated within the European Union (Directive 2003/99/EC and Decision 2013/652/EU). In particular, this system harmonises the surveillance schemes between each Member State. In France, ANSES is the National Reference Laboratory for antimicrobial resistance. As such, it monitors bacterial resistance in the food chain, according to the protocol established by the European Directive. It therefore carries out annual surveillance plans, overseen by the Directorate General for Food (DGAl), which are used to monitor developments at national and European level.

Monitoring meat for consumption

The targeted bacteria are isolated from samples taken from healthy animals in slaughterhouses, from intestinal contents and carcasses. Every year, the antibiotic susceptibility of the isolated strains is measured by ANSES. The results are published in France in the DGAL's report on monitoring and control plans. At European level, they are provided in a report by the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC), published in year n+2.

The European results for 2019 should therefore be available sometime next year.
Surveillance is organised alternately every two years: in poultry (broilers, layers and turkeys) in even years and in slaughter animals (cattle and pigs) in odd years. The bacteria monitored are *Campylobacter jejuni*, *Salmonella spp*. and *Escherichia coli*.



Results for pigs

- Between 2009 and 2019, resistance levels declined for several monitored antibiotics: the proportion of resistant bacteria **fell** from 74.7% to 51.1% for tetracycline, from 65.2% to 35.1% for sulfamethoxazole, and from 37.3% to 29.8% for trimethoprim.

- At the same time, resistance to other antibiotics has **increased**: this was the case with ampicillin, to which 30.3% of the isolated bacteria were resistant in 2019, and with antibiotics of the quinolone class, to which resistance increased from 1.9% in 2009 to 4.3% in 2019.

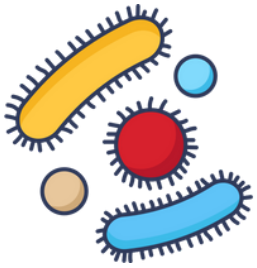
Results for calves

Because surveillance only began in 2015, there are still too few measurement campaigns to make interpretable statistical analyses. Nevertheless, the following observations were made:

- a **fall in levels of resistance** to most of the antibiotics tested.
- However, there were two **exceptions** to this trend: chloramphenicol, for which levels were fairly stable, and gentamicin, for which resistance levels increased very slightly.

A diminishing number of bacteria resistant to at least one of the antibiotics tested

Over the surveillance period (11 years for pigs, 5 years for calves), the number of strains susceptible to all the antibiotics tested has increased significantly, from 12% in 2009 to 29.8% in 2019 in pigs, and from 24.3% in 2015 to 39.9% in 2019 in calves: there are therefore fewer and fewer bacteria resistant to at least one of the antibiotics tested.



Less resistance to critically important antibiotics

Since 2015, strains of *Escherichia coli* resistant to third-generation cephalosporins, a class of critically important antibiotics, have been specifically screened for in the intestinal contents, especially caeca, of animals at slaughter and in meat for distribution. Very few resistant bacteria were found in either pork or beef. Their presence was higher in caeca, but did not exceed 30% of the samples analysed and this rate has been decreasing since surveillance began.

Salmonella posing a threat to humans are still susceptible to antibiotics

The antibiotic susceptibility of Salmonella was measured for strains isolated from both animal species. The level of antimicrobial resistance varied according to the serovar, i.e. the set of antigenic characteristics of the strains identified. However, the predominant serovars and those constituting a Category 1 health hazard, which are considered a threat to human health, remain susceptible to the main antibiotics tested.

4 A pioneering review of knowledge on antimicrobial resistance and antibiotics in the environment

While antimicrobial resistance is a well-researched phenomenon in humans and animals, its dissemination in the environment is less well known. However, certain resistance genes that are currently a problem in medicine come from bacteria in the environment. ANSES was therefore asked to conduct an expert appraisal of the state and possible causes of contamination of aquatic and terrestrial environments in France by antibiotics, of resistant bacteria that are pathogenic for humans and of antimicrobial resistance genes. It also examined the mechanisms that promote the emergence and persistence of antimicrobial resistance in the environment.
This is one of the very first reviews of knowledge on this issue. To carry out its work, the Agency drew on the scientific literature and the results of research conducted in France on environmental contamination, in particular that funded by ANSES as part of the National Research Programme for Environmental and Occupational Health (PNR EST).

Contamination of the environment by antibiotics is due to human activities

Antibiotic concentrations in France are low, regardless of the setting. The antibiotics found most frequently in the environment are those that degrade the least, and are not necessarily the most widely consumed. The main sources of environmental contamination by antibiotics are related to human activities: discharges of treated wastewater and the spreading of sewage sludge and livestock manure. Antibiotics found in water are therefore in higher concentrations downstream of wastewater treatment plant discharges than upstream. There are fewer data on soil contamination, and these only concern agricultural spreading sites. The antibiotics and concentrations found depend on the spreading type.

The antibiotics found most frequently in the environment are those that degrade the slowest

Resistant bacteria that disappear faster than genes

Antibiotics, resistant bacteria and resistance genes have the same contamination sources. Concentrations of resistant bacteria and resistance genes decrease the further they are from the source of contamination, whether this is a treated wastewater discharge or a spreading site.

Although the treatments used on wastewater and spreading products can reduce the quantities of resistant bacteria and resistance genes released into the environment, they are not designed to eliminate them completely.
The antimicrobial-resistant bacteria studied are mainly of faecal origin. They have difficulty surviving in the environment and are mainly found at sites heavily contaminated by human activities. Resistance genes can persist longer, either outside cells or harboured by other bacteria not considered by the studies.

Study of the mechanisms that can promote the survival of resistant bacteria

ANSES's work also examined the environmental factors that may promote the selection of antimicrobial-resistant bacteria and the transmission of resistance genes. Few data are available on this subject. In general, it seems that the quantities of antibiotics found in the environment in France are too low to promote the survival of resistant bacteria and the persistence of resistance genes. In addition, their fate in the environment may be influenced by the presence of trace metal elements or biocides, the diversity of bacterial communities and the heterogeneity of the settings.

Improving the monitoring of environmental contamination and continuing to acquire knowledge

The results obtained are likely to evolve with climate change and developments in practices related to the circular water economy, such as the reuse of treated wastewater or artificial recharge of aquifers. These phenomena could indeed modify the routes of introduction and spread of antibiotics and resistant bacteria in the environment and affect its ability to dissipate this anthropogenic contamination.

To improve the comparison of data, ANSES recommends that all studies on antimicrobial resistance in the environment should monitor a set of indicators including several antibiotics, a specific resistant bacterium and a specific resistance gene. The Agency also suggests that these studies should take into account the fate of this contamination over time and spatially. Lastly, ANSES recommends consolidating and broadening current knowledge, whether on environmental contamination by antibiotics, bacteria and resistance genes, on the factors promoting their spread, or on the assessment of the ability of ecosystems to dissipate contamination.

See ANSES Opinion and Report on "Antimicrobial resistance and the environment " (in French)

5 Research on antimicrobial resistance: a project to predict the transmission of antimicrobial resistance genes

The project's objectives

Most of the genes that enable micro-organisms to resist antibiotics come from bacteria in the environment. As from next January, ANSES will be taking part in the **PRE-EMPT** research project on high-throughput identification of antibiotic resistance progenitors across interconnected settings. This study will seek to anticipate the risk of spread of antimicrobial resistance genes.

Its novel approach is based on the non-targeted searching for links between resistance genes and mobile genetic elements that can potentially be transmitted between bacteria, and the microbial species that carry them. The results should make it possible to develop indicators of the risk of transmission of a resistance gene to a bacterium of importance to human or animal health. To do this, it will use the most recent genomic, metagenomic and functional approaches, in order to gain a comprehensive view of all the genes of the organisms found in a given environment and the roles they play.

Organisations involved: ANSES (Antimicrobial resistance and bacterial virulence unit), INRAE, Institut Pasteur and Inserm.

Funding: Budget of €415,000, funded by the French National Research Agency (ANR), under its 2020 generic call for projects.

Duration: 3 years

Anticipate the risk of spread of antimicrobial resistance genes.

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