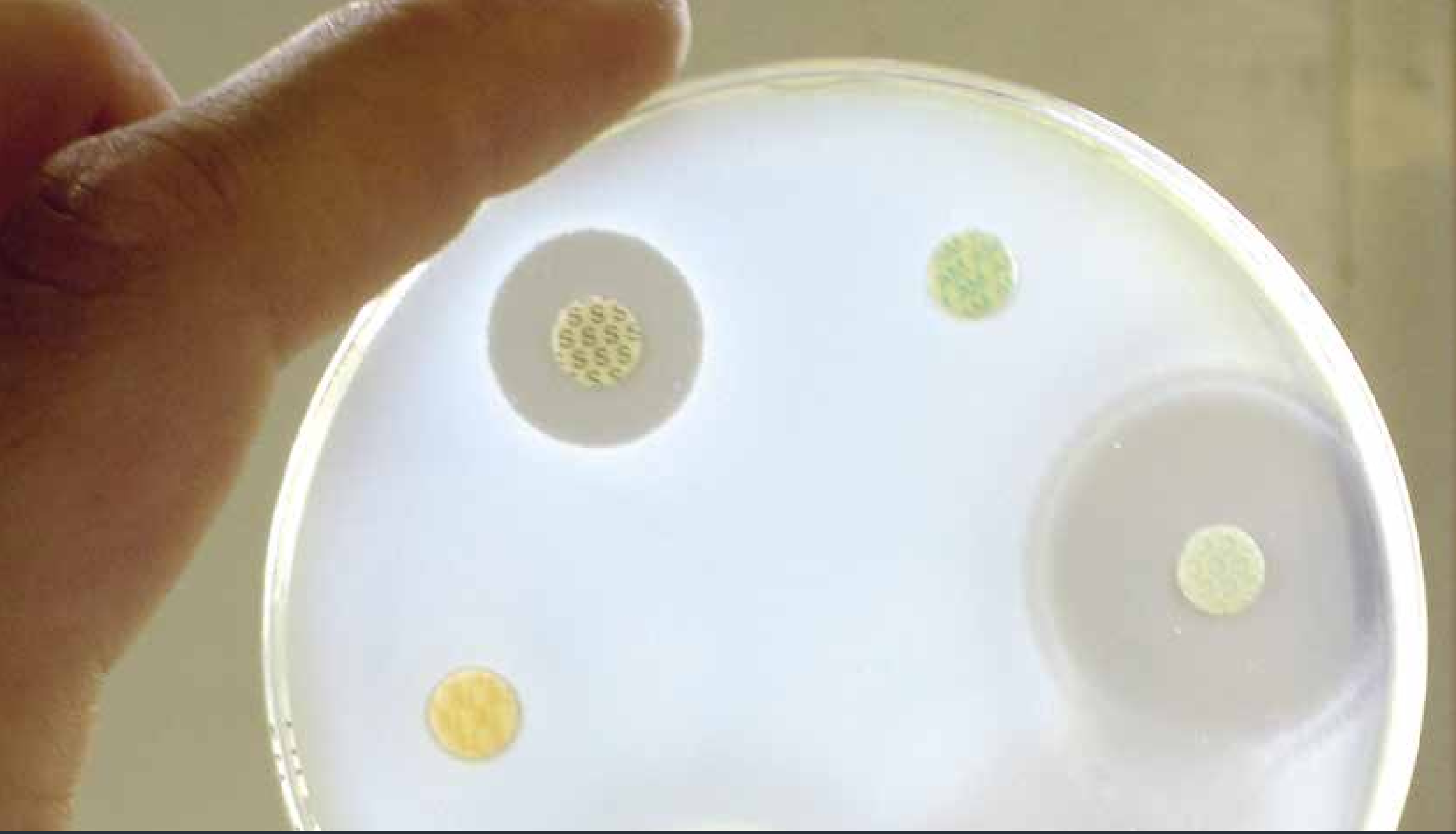
REDUCING ANTIBIOTIC USE IN THE LIVESTOCK INDUSTRY

INRA
SCIENCE & IMPACT

PRESSE Dossier



Antibiotic susceptibility testing via agar diffusion (disk diffusion method).

A BRIEF HISTORY OF ANTIBIOTICS... AND OF ANTIBIOTIC RESISTANCE

The discovery of antibiotics changed the course of medicine and has saved millions of lives. However, their misuse over recent decades has led to the emergence of antibiotic resistance. Indeed, it is now difficult to cope with certain bacteria for which antibiotics are the sole treatment available. More than ever, it is crucial to reduce antibiotic use and to scrupulously follow prescription directions. In 2002, the French government began launching a series of national programmes aimed at raising awareness about antibiotic misuse; varying levels of success have been achieved. The agricultural industry is the greatest consumer of antibiotics but is also strongly engaged in the fight against antibiotic resistance.

ANTIBIOTICS ARE AMAZING!

Alexander Fleming, a biologist, discovered antibiotics in 1928. As the story goes, he came back from vacation to find that certain Petri dishes containing cultures of staphylococcus bacteria had not been properly soaked in the disinfectant bath meant to clean them. They were covered with mold. When he took a closer look, he also saw that the mold appeared to have repelled the bacteria. The mold was identified as *Penicillium notatum*, so Fleming named the antibacterial agent "penicillin". However, it was not until the Second World War that this important discovery was put to full use. Thanks to the work of Howard Florey, Ernst Chain, and Norman Heatley, penicillin was produced at large scales from a strain of *Penicillium*. This medication was used to treat many injured soldiers and to fight the bacterial infections that went hand in hand with wartime conditions. After the end of the war, penicillin spread throughout the world, and, very quickly, other antibiotics were developed. They were employed to treat often fatal infectious diseases such as tuberculosis, plague, syphilis, and cholera. For this reason, antibiotics are likely one of the greatest discoveries in the history of medicine. However, from the very beginning, scientists observed that certain bacteria were resistant to antibiotics. When Alexander Fleming received the Nobel Prize in 1945, he expressed clear concern about antibiotic resistance. In particular, he warned against the risks of antibiotic misuse, namely administering antibiotics at low doses, which would allow bacteria to both acquire resistance and pass it along to others, thus rendering treatments ineffective.

CATASTROPHIC MISUSE

Research carried out in the US in the late 1940s showed that giving very low doses of antibiotics to livestock such as poultry and swine improved their growth. Faced with the food crisis, scientists around the world, including at INRA (founded in 1946), were focused on developing better crop and livestock practices to achieve higher yields. This discovery was thus put to immediate use. Antibiotics were no longer viewed as medication. Instead, they were treated as growth-enhancing food supplements. During this same time period, antibiotic resistance was observed in pathogens of animal origin (e.g., salmonella bacteria), and the Swann Report was published, which warned against the consequences of antibiotic misuse. This report, which came out in 1969, recommended that antibiotics only be used when medically necessary. However, it was not until 2006 that employing antibiotics as growth factors was prohibited in the EU (it remained legal in the US).

ECOANTIBIO

Does this mean that France is addicted to antibiotics? No, and there are actually reasons to be optimistic about change. In 2011, the French Ministry of Agriculture unveiled Ecoantibio 2017, an extremely ambitious programme whose aim was to reduce antibiotic use in the livestock industry by 25% over a five-year period. All the industry's stakeholders were asked to take part, including farmers, veterinarians, public research institutes (like INRA), and policy-makers. The programme had five main pillars:

› **PILLAR 1:** Promote safe practices and educate stakeholders
› **PILLAR 2:** Develop alternatives to antibiotics
› **PILLAR 3:** Improve supervision of practices and enforcement of commercial prescription rules
› **PILLAR 4:** Improve monitoring of antibiotic consumption and antibiotic resistance
› **PILLAR 5:** Encourage equivalent strategies at the European and international level.

The programme was a great success. From 2012 to 2016, antibiotic use dropped by 37%, which is 12% more than the targeted amount. The even better news is that the use of fluoroquinolones and cephalosporins declined by 75% and 81%, respectively. Usage of these two crucial classes of antibiotics became subject to regulation in 2016. However, these advances do not mean we can rest on our laurels. This work is just the beginning. Indeed, the second Ecoantibio programme (2017-2021) comprises four pillars that are focused on educating stakeholders and helping them adopt new practices that better align with the global One Health approach:

› **PILLAR 1:** Develop methods for preventing infectious diseases and facilitate the use of alternative treatments
› **PILLAR 2:** Educate stakeholders about key issues in the fight against antibiotic resistance, the reasonable use of antibiotics, and other methods for controlling infectious diseases
› **PILLAR 3:** Share a variety of tools—make available tools for evaluating and monitoring antibiotic use as well as tools for ensuring that antibiotics are prescribed and administered responsibly
› **PILLAR 4:** Share responsibility—ensure that rules regarding responsible use are being properly applied at the national level and encourage the establishment of similar rules at the European and international level.

RAISING AWARENESS

Antibiotic misuse in human medicine has also contributed to the spread of resistance. Doctors that irresponsibly prescribe antibiotics or patients that do not take their prescriptions as required (remember Fleming's warning about low doses)—these are just two situations that have contributed to the emergence of multidrug-resistant bacteria, for which treatment options are limited. Furthermore, pandrug-resistant bacteria are now being observed in hospitals; these are bacteria that are resistant to all available antibiotics. It is crucial to act now because we are faced with the prospect of being unable to treat certain bacterial infections or, worse, witnessing the reemergence of certain diseases. In 2002, a French national programme to promote responsible antibiotic use was launched. The slogan was "Antibiotics are not automatic". Consumption of antibiotics dropped by nearly 20% as a result. Unfortunately, since 2010, sales have been climbing again, despite the implementation of a new government programme. The new slogan? "The more we use antibiotics, the more we lose antibiotics".

ONE HEALTH

The One Health approach recognises that inextricable connections exist among animal health, human health, and the environment. As a result, no one component can be considered individually. This reality is immediately apparent when we look at antibiotic resistance. As you will discover in this report, resistant bacteria occurring in livestock can easily jump to humans or spread throughout the environment. Furthermore, this movement is multi-directional. If the One Health concept still seems abstract, let us take a look at a concrete example. Certain varieties of meat chickens are loaded with salmonella bacteria, but the animals never develop clinical signs of disease. However, consumers can contract salmonella, a potentially fatal disease, from eating an egg produced by one of these chickens. If the infection is caused by antibiotic-resistant bacteria, then the situation can get a lot worse. Consequently, limiting antibiotics and promoting the use of alternative treatments in the livestock industry is a crucial part of controlling the emergence of antibiotic-resistant pathogens that are transmitted to humans (e.g., via the consumption of milk, meat, or eggs) or that circulate within the environment (e.g., via the faeces or saliva of infected animals or liquid fertiliser spread in fields). These pathogens can also be transmitted to other animals in the herd, which can spread the bacteria in turn. The One Health approach is perfectly suited to these sorts of situations because it calls upon all stakeholders in the fields of human health, animal health, and environmental stewardship to work together to find solutions in the fight against antibiotic resistance. INRA has long adopted this approach in the form of multidisciplinary projects. For example, the Animal Antibiotics Research Network (R2A2) has brought together researchers working on fundamental research, applied research, and the social sciences.

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ANTIBIOTIC RESISTANCE: UNIFIED ACTION FOR A SHARED PROBLEM

It is crucial to reduce antibiotic use to limit the emergence and spread of multidrug-resistant bacteria. This task will require raising awareness and radically changing current practices to align with the One Health approach. To facilitate this transition, INRA has launched numerous initiatives that encourage researchers from different scientific disciplines to carry out joint research projects that also involve stakeholders in the agricultural industry.

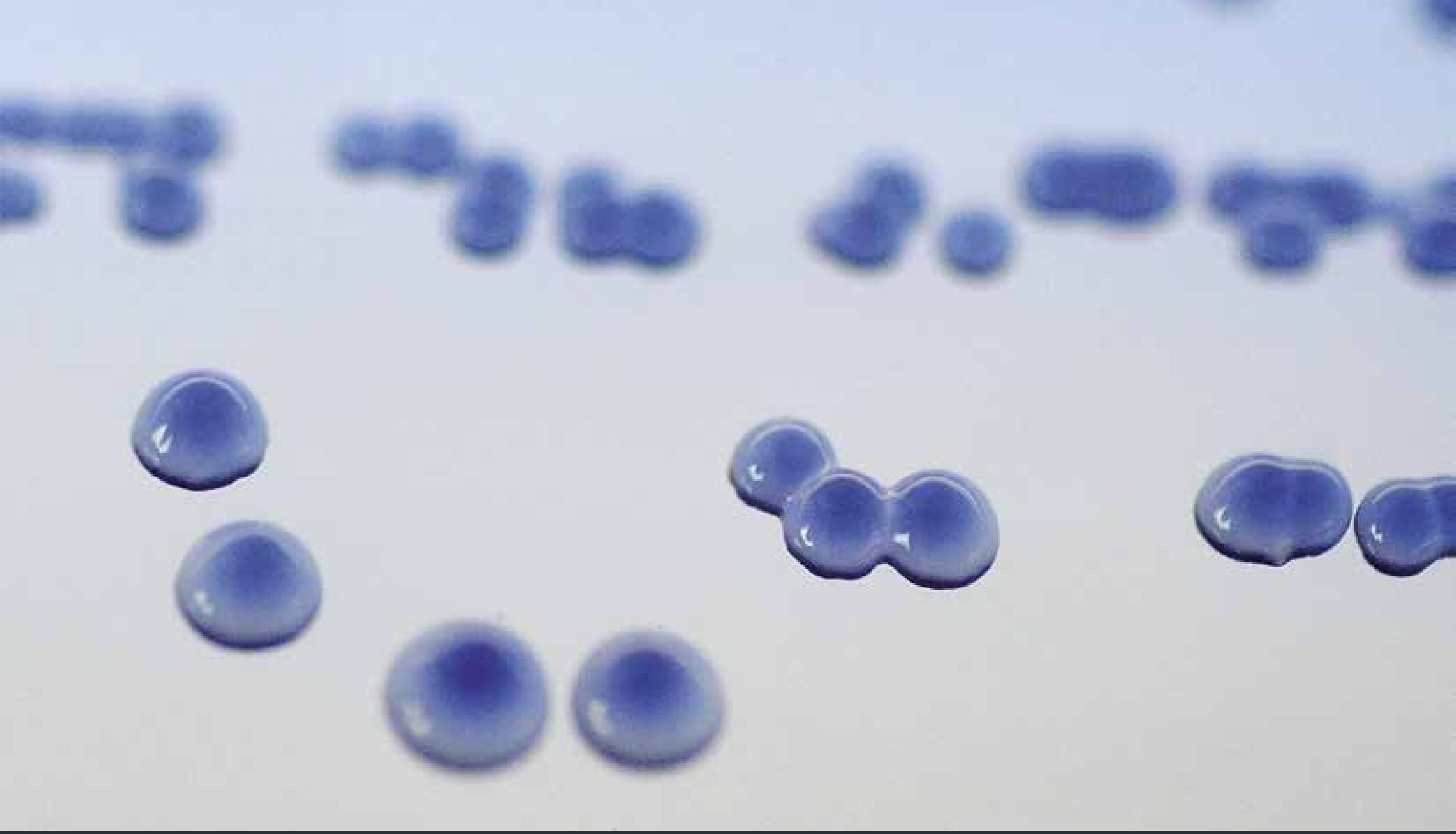
R2A2: A THINK TANK FOCUSED ON ANTIBIOTIC RESISTANCE

Created in 2013, the Animal Antibiotics Research Network (R2A2) is a multidisciplinary research team. Funded by the INRA metaprogramme Integrated Management of Animal Health (GISA), it has a clear objective: to reduce antibiotic use in veterinary medicine with a view to controlling the emergence and spread of resistant bacteria. R2A2 holds meetings several times per year that focus on different subjects. For example, topics of discussion have included why livestock farmers fail to implement preventive measures, the relationship between the microbiota and health, and antibiotic use in the rabbit industry. Meeting participants—sociologists, geneticists, infectious disease specialists, nutritionists, pharmacologists, epidemiologists, veterinarians, livestock farmers, technical experts, and stakeholders with economic interests—talk about the target topic, share research ideas, and design suitable projects. These meetings bring together individuals and industries that rarely rub shoulders and have given rise to several initiatives. An example is the OMAP project (Optimizing metaphylactic use of antimicrobials in poultry), which examines the practice of metaphylaxis * on poultry farms by combining perspectives from the social sciences, epidemiology, pharmacology, and the clinical sciences. The project's complementary objectives are threefold: 1) to identify the technical and sociological factors that influence antibiotic use on farms; 2) to develop innovative early-detection systems for health problems based on precision medicine; and 3) to optimise antibiotic use so as to prevent the administration of overly high or overly low doses, which both contribute to the emergence of resistance. Another noteworthy project is TRAJ *(Trajectoires de changement dans l'utilisation des antibiotiques en élevage)*, which sought to change how antibiotics are used by the livestock industry. PSYCHO, funded by Ecoantibio 2017, expands on TRAJ's work, by carefully examining the psychological and social factors linked to changes in antibiotic use in the poultry industry. R2A2 is now turned towards new challenges, namely studying the progress that has been made in reducing antibiotic use in the swine and rabbit industries. For the first time, it will also look at the use of antibiotics in the aquaculture industry.

* Metaphylaxis is defined as the treatment of an entire group of animals following the appearance of clinical signs of infection in a few animals.

SOCIAL SCIENCE TACKLES VETERINARY CHALLENGES

How did we arrive at this state of affairs? How did the norm become intensive agriculture, a system in which there has been widespread misuse of antibiotics, including using antibiotics as growth factors (at least until recently)? How did dependence on antibiotic sales become entrenched in the veterinary field? Indeed, following regulatory changes (i.e., the French law of May 29, 1975), only veterinarians can prescribe medications for livestock industry, and, at present, 60–90% of their earnings come from these prescriptions. Finally, how can simultaneous action be taken to allow veterinarians to become less dependent on antibiotic sales and limit antibiotic use in livestock? These are all issues that the project AMAGRI (Antimicrobials in agriculture: actors, practices, conflicts) is tackling; this work is headed by six researchers in the social sciences. Project collaborators include historians, sociologists, political scientists, and economists. The project has three objectives. The first is to retrace the history of antibiotic use from 1975 to 2011, when the first Ecoantibio programme was launched, to better understand the ties among the policies implemented over the last 40 years and their role in the emergence of antibiotic resistance. The second is to identify ways for veterinarians to become less dependent on antibiotic sales. Solutions currently being studied include the creation of new services, changes in the way their work is organised (e.g., creating joint practices), or charging for work that they have previously done for free because they would be compensated via antibiotic sales. The third is to examine changes in the relationships among stakeholders in the cattle, swine, and poultry industries and attempt to identify approaches for further reducing antibiotic use. AMAGRI builds on the work done by TRAJ (2014–2016), which explored the technical, economic, and social reasons that antibiotics are used for managing animal diseases. In particular, INRA researchers took a closer look at livestock farmers who were at the forefront of efforts to reduce or eliminate the use of antibiotics. The goal was to understand their motivations, their techniques, whether or not they received help, and the challenges they faced.



Streptococcus salivarius colonies.
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UNDERSTANDING RESISTANCE MECHANISMS

Antibiotic resistance is a complex problem. This is not a surprise given that bacteria have been evolving for millions and millions of years—adapting to environmental conditions and developing new ways of acquiring resources, reproducing, and surviving. Indeed, it has only taken them a few years to respond to our control methods because they can exploit strategies they had previously developed to deal with their natural enemies. INRA researchers are untangling the frequently sophisticated ways in which bacteria resist antibiotics and transmit that resistance to other bacteria, some of them pathogens.

BACTERIAL CONJUGATION: A KEY MECHANISM BEHIND THE SPREAD OF ANTIBIOTIC RESISTANCE

Most of the antibiotics that we use are naturally present in the microorganisms found in our environment. As we saw, penicillin comes from a fungus. Therefore, it is not surprising that, over evolutionary time, bacteria (including pathogenic bacteria) have evolved ways to resist the attacks of other microorganisms, including the deployment of antibiotics. These adaptations have been passed along across generations. However, bacteria also have less traditional ways of acquiring and transmitting resistance. For example, they can use horizontal gene transfer, which can occur via conjugation, transformation, or transduction. Let us take a look at conjugation, the most commonly employed mechanism. Most bacteria contain plasmids, which are circular pieces of DNA that can replicate independently of the chromosome. Plasmids are mobile genetic elements and can contain one or more antibiotic-resistance genes. Some have such a broad suite of these genes that the bacteria are pandrug resistant, which means that they are resistant to all available antibiotics. In conjugation, a bacterium physically transfers DNA, most often a plasmid, to another bacterium. If the plasmid carries antibiotic-resistance genes, then the original bacterium's resistance is passed along as well. In turn, the recipient bacterium can now pass along copies of the plasmid to others. This mechanism facilitates the rapid spread of resistance within bacterial communities (i.e., the microbiota), which can diminish the chances of successfully treating infections with antibiotics.

EXPERIMENTALLY CHARACTERISING RESISTANCE RISKS

At the INRA Centre of Val de Loire, researchers are studying the spread of antibiotic resistance in chickens. They are not conducting this work on farms. Instead, the centre has experimental facilities dedicated to poultry research. The benefit of this set-up is that different elements of the industry are represented, from egg laying to broiler production. It also provides ideal conditions for characterising natural bacterial resistance, studying both vertical and horizontal pathogen transmission dynamics, and determining how the environment affects transmission. Here, vertical transmission consists of the transfer of resistant bacteria from chickens to their offspring, whereas horizontal transmission involves the exchange of resistant bacteria among poultry of the same cohort. This work will help identify agricultural practices that promote or hinder the spread of antibiotic resistance.

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ANOTHER REASON SUGAR IS BAD FOR HEALTH

INRA researchers recently discovered a type of plasmid in possession of both antibiotic-resistance genes and a mechanism for metabolising certain sugars, which could promote growth and the transfer of resistance in bacterial pathogens. This is bad news because these sugars have been used for years as prebiotics*! They are administered to animals with digestive problems and have been shown to have positive effects on commensal flora. The question thus arises: is the cure worse than disease? Researchers are looking for the answer. As part of the PLASMEQUI project, scientists will examine how the use of these prebiotics affects the presence, spread, and amplification of this plasmid type by comparing results for horse farms that use prebiotics versus those that do not.

* A prebiotic is defined as fibrous dietary material that specifically promotes the growth and/or activity of gut bacteria. It can contribute to host health and well-being.

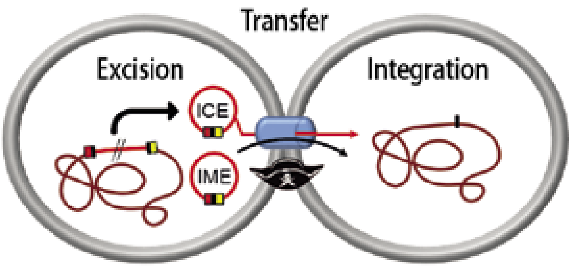
CAN PHAGES VECTOR ANTIBIOTIC RESISTANCE?

In 2014-2015, a series of studies spurred heated discussion within the scientific community. Researchers had discovered antibiotic-resistance genes in the genomes of certain bacteriophages (i.e., viruses that infect bacteria). This news was quite alarming because phages frequently hop between bacteria. This element adds further complexity to a situation already made complicated by plasmid-mediated transfer of resistance. It has long been known that phages could transfer genes from one host to another, through a process known as transduction. However, transduction appears to take place accidently. In around 1 out of 10,000 cases, a phage will incorporate a piece of host DNA into its own genome and depart with it. Given the potential seriousness of the situation, several research teams, including some at INRA, decided to carry out a fine-scale analysis of all known bacteriophages, to identify any bacterial antibiotic-resistance genes they might be carrying. The fact is, they did not find a single one! This discrepancy between the two sets of findings may have been due to the tremendous computational requirements of the initial studies. So that the analyses did not run for inordinate amounts of time, the focus was on very small DNA fragments. It is therefore possible that some extrapolation took place, giving rise to the alarming results. INRA published the results of its work in 2016, providing a certain level of reassurance, at least for now. However, phages are naturally good at acquiring new genes. If they currently do not carry around antibiotic-resistance genes, it is likely because they fail to derive any benefits. In this system, it is important to understand that many phages do not kill their bacterial hosts. Instead, they live with them in symbiosis. Consequently, it could be helpful for phages to provide their hosts with antibiotic resistance, in the interests of enhancing their own survival. However, to date, this phenomenon has yet to be observed.

Colonies of different bacteria: the large ones are *Lactobacillus casei*, the medium-sized ones are *Streptococcus salivarius subsp. thermophilus*, and the small ones are *Bifidobacterium species.*

BUILDING AND EXPLOITING

During conjugation, there are two general types of mobile genetic elements (MGEs) that can be transferred in addition to plasmids. The first category comprises integrative and conjugative elements (ICEs), which encode the functional components of the conjugation machinery: they generate the physical connection that allows DNA (including themselves) to pass from one bacterium to another. The second category is composed of integrative and mobilisable elements (IMEs), which are opportunistic in nature. They take advantage of the machinery created by ICEs to move between bacteria. Both can help spread antibiotic-resistance genes.

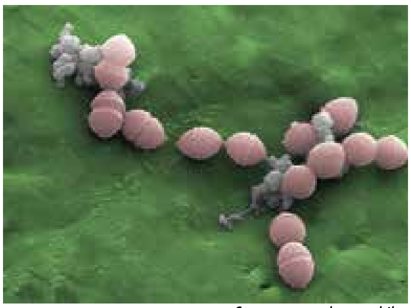


TAKING STOCK

The genus *Streptococcus* contains a vast number of members. Some species are obligate pathogens like *Streptococcus suis*, which is transmitted to humans by infected swine or wild boars. Others are opportunistic pathogens* like *S. agalactiae*. There are also commensals *(S. salivarius)* and streptococci that help with food production (*S. thermophilus*; used to create yogurt). All these bacteria can occur simultaneously within our bodies, which means that they can also exchange genetic material, notably via conjugation. Researchers from INRA and the University of Lorraine have spent several years studying the mechanisms underlying gene transfer in streptococci and, more specifically, the transfer of antibiotic-resistance genes. A key part of this work has been characterising the MGEs that are present in different *Streptococcus* species. To accomplish this task, they established a collaboration with INRIA and the INRA Research Unit for Applied Mathematics and Computer Science from Genomes to the Environment. Together, they developed a bioinformatics tool, ICE-Finder, which automated and thus accelerated the search for ICEs and IMEs in the thousands of genomes available. The researchers discovered that MGE diversity was much higher than expected and that a large number of MGEs were carrying antibiotic-resistance genes. The question arose: why are ICEs and IMEs excising themselves from the DNA of a given host to incorporate themselves into the DNA of another host? Scientists are currently looking for the answer. Some studies have shown that certain antibiotics can damage DNA, which induces stress and leads to element excision. However, more research is needed to clarify the mechanism. Ultimately, the ability to interrupt or control this process could be useful.

* An opportunistic pathogen is a micro-organism that does not normally cause disease but that can become pathogenic given the right set of circumstances, such as weakened host immune defenses or resistance.

WHEN GOOD BACTERIA SHARE BAD GENES



Streptococcus thermophilus

Transformation is a process by which bacteria can take up DNA from their surroundings via their cell membranes. Bacteria with this capacity are referred to as "competent." Transformation is associated with competitive advantages, such as the ability to exploit nutrients that fellow bacteria cannot. Indeed, researchers have found that milk contains very small quantities of free DNA carrying antibiotic-resistance genes. Could such genetic material be picked up by competent non-pathogenic bacteria, such as *S. thermophilus*, a species that is used to make yogurt and various cheeses? Yes, but probably not very easily. Research was carried out using free DNA from antibiotic-resistant pathogenic streptococci. It was found that transformation did not take place—the resistance genes were not incorporated into the host's chromosome. That said, we do observe antibiotic-resistance genes in bacteria like *S. thermophilus*. Consequently, it is unclear how the genes are acquired. Perhaps they represent sequences other than those tested. It may also be that they are transferred in two ways: by conjugation, via plasmids, or by transduction, via bacteriophages. Scientists are continuing to explore these issues, driven by a common objective—to understand the underlying mechanisms with a view to inhibiting them.

SEWAGE SLUDGE CAN SPREAD ANTIBIOTIC RESISTANCEE

In France, it is common practice to use sewage sludge resulting from wastewater treatment as fertiliser on agricultural lands. Sewage sludge contains important nutrients such as phosphorus and nitrogen, thus providing an alternative to mineral fertilisers, as well as organic matter, which enriches the soil. Unfortunately, it also contains organic compounds, heavy metals, and potentially antibiotic-resistant bacteria and antibiotic-resistance genes, which can all contaminate the ecosystem (i.e., soil, water, plants, animals, and humans). Each year, around 7 million tonnes of fresh sewage sludge are used as fertiliser. That is a drop in the bucket compared to the 300 million tonnes of livestock effluent (e.g., manure, slurry) used, which can also contain antibiotics! However, sewage sludge contains a broader range of organic compounds and antibiotics because it is produced using both domestic and industrial wastewater. Several researchers have shown that using sewage sludge as fertiliser helps spread antibiotic resistance. However, how does this happen and what are the consequences? This question is the basis of MADSludge, an INRA project that seeks to make improvements to the wastewater treatment industry to limit the diffusion of antibiotics and the spread of antibiotic resistance. In one experiment, researchers added antibiotics to raw sludge and then treated the sludge using the various methods employed by wastewater treatment plants (i.e., drying, application of lime, anaerobic digestion, composting, and anaerobic digestion plus composting). They then placed both the treated sludges and a control sludge between two layers of soil. The sludges were left to incubate in individual bags that allowed biological and chemical interactions with the environment. The researchers monitored trends in antibiotic resistance in the soil and the sludges over the subsequent year. More specifically, they regularly took samples of the soil and sludges to determine how sludge treatment affected the spread of antibiotic resistance in the soil as well as the degree of soil resilience. They characterised gene transfer dynamics to determine if antibiotic-resistant bacteria in the bags were passing along their resistance to soil bacteria, and vice versa. In the long term, researchers hope to develop guidelines for proper sewage sludge usage by farmers—for example, being able to recommend a sludge type based on specific fertiliser needs (determined by soil type or crop type, for example).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SOURCING THE FECES YOU CONSUME

Baby rabbits eat their mothers' faeces. This type of behaviour (i.e., coprophagy) has been observed in several animal species. For example, piglets eat 20 grams of faeces per day during the weaning period. Indeed, coprophagy plays a rather important role. In the context of antibiotic resistance, it serves to transmit antibiotic-resistance genes occurring in the intestinal microbiota from one generation to the next. And there may be many to transmit. In a recent genomics study, INRA researchers identified more than 100 antibiotic-resistance genes in faeces taken from 13 female rabbits coming from farms all across France. Twelve of these genes occurred in all the animals, even those that came from farms on which no antibiotics had been used in the last eight years. There was variability in bacteria abundance among individuals: both very high and very low numbers of resistant bacteria were found in the faeces samples. The scientists then carried out a study in which some baby rabbits from mothers whose microbiota contained large numbers of resistant bacteria were fed faeces from females with low levels of resistant bacteria. As expected, these baby rabbits developed a microbiota in which resistant bacteria were less common, as compared to the rabbits allowed to consume their mothers' faeces. There is an additional advantage: because antibiotic-resistance genes were less common in their microbiota, it would be easier to treat such rabbits with antibiotics in the case of an infection. However, the process of switching the faeces supply is labour intensive. As a result, this technique is not in the economic interests of farmers, even if it could clearly help limit the spread of antibiotic-resistant bacteria, including to humans. To nonetheless encourage its use, the researchers are studying how to improve upon already healthy microbiota. For example, the addition of certain beneficial bacteria could enhance rabbit growth. If the technique improved rabbit health and growth while presenting economic, environmental, and public health benefits, then the animals' enhanced survival and growth would compensate for the increased labour costs.


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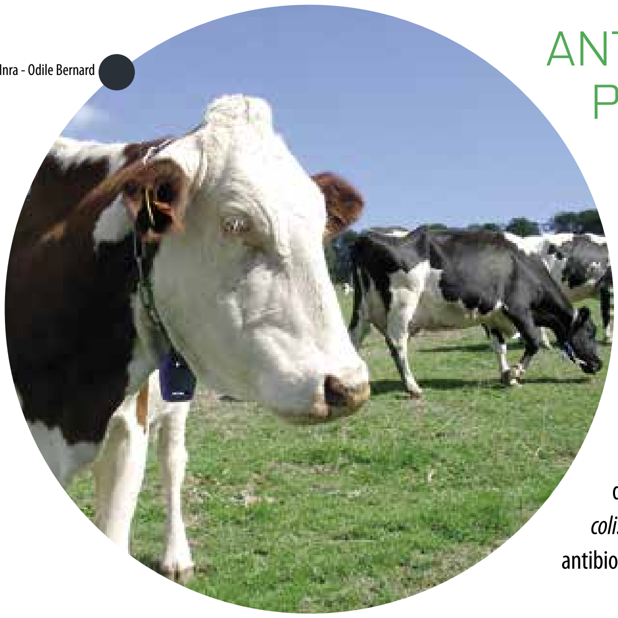
REDUCING ANTIBIOTIC USE

Antibiotics are indispensable. They are also the most effective way, and sometimes the only way, to deal with certain livestock diseases. It is important to use them properly and strictly when necessary. To reduce their usage, and thus limit the emergence of antibiotic resistance, there are several promising approaches: vaccination, breeding programmes, and individual monitoring.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ANTIBIOTICS: PREVENTIVE TREATMENTS ARE NOT ALWAYS HEALTHY

Thanks to the work of Ecoantibio 2017, we witnessed a dramatic reduction in preventive antibiotic treatments. Unfortunately, such practices die hard. Some farmers still give antibiotics to dairy cows during the dry period, which is when cows are not milked to allow them to rest before the next calving period and lactation cycle. They administer an intra-udder antibiotic treatment with a view to eliminating any potential pathogens and thus reducing the risk of mastitis. The dairy industry is not alone in clinging to such practices. In the pork industry, for example, antibiotics are still given during the weaning period, to lower the risk of diarrhoea induced by *Escherichia coli*. Unfortunately, this approach is not always effective, and this improper use of antibiotics contributes to the emergence and spread of antibiotic resistance.

ANIMALS UNDER SUPERVISION

Established in early 2018, the Joint Research Unit for Innovative Treatments and Resistance (InTheRes) aims to reduce the use of antibiotics and antiparasitics in veterinary medicine. To tackle this tremendous challenge, researchers are focused on two main tasks: furthering the development of precision medicine and optimising treatment strategies. One objective is to end the use of metaphylaxis, which is when an entire group of animals is treated when a limited number of its members become sick. This extreme method has benefits because the likelihood of eliminating the infection is stronger if antibiotics are deployed the moment any signs of disease appear. However, it also has disadvantages because, by treating the healthy animals (and thus more animals than necessary), there is a greater chance that antibiotic-resistant bacteria will emerge and spread. A safer approach would be to identify infected animals from the first moment they show signs of disease and make sure that they are treated immediately. Success would therefore rely on carefully monitoring each and every animal. This is the perfect job for mathematicians at INRA and the National Veterinary School of Toulouse. Sensors installed on watering troughs and feed troughs and attached to the animals themselves are being used to capture large amounts of data. The mathematicians will exploit this information to characterise normal and abnormal animal behaviour. For example, a cow might drink too much or too little, a pig might display odd movements, or a sheep's body temperature might rise or fall in an atypical way. However, dealing with meat chickens in intensive farming systems is a bit more complicated. It would be impossible to equip thousands of poultry with electronic chips. However, the birds can be closely monitored using both video footage and algorithms that track and analyse the behaviour of individual animals.

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OPTIMISING THE USE OF ANTIBIOTICS

While approaches involving Big Data and artificial intelligence are amazing tools to deploy upstream, they will not put an end to antibiotic use. Antibiotics will always be important, and often indispensable, in treating infections. However, it is possible to use them more effectively. This is the other research focus of InTheRes. We know that longer treatments translate into higher risks that antibiotic resistance will emerge. InTheRes researchers want to develop a commando-style treatment, which strikes hard and fast but leaves no trace of its passage. This objective could be achieved by combining antibiotics with other medications, such as bacteriophages or anti-virulence compounds. Or, once the pathogen has been identified, two antibiotics with different modes of action can be used simultaneously. If one faces bacterial resistance, the other may still be operational. The researchers are also looking at combining antibiotics with probiotics or essential oils, with a view to establishing or re-establishing balance in the intestinal microbiota either before or after treatment.

THE GENETICS OF DISEASE RESISTANCE

Almost all traits are underlain by genetic variability. In livestock, examples of this variability include differences in animal size, robustness, reproductive capacity, milk production, milk fat content, and disease resistance. However, genetics are not everything. The manifestation of a given trait is shaped both by genetics and environmental conditions. Heritability expresses the degree to which genetics explain a given trait. In most cases, heritability is less than 50%. When it comes to disease resistance, heritability is often very low (2–15%), which underscores that environmental conditions largely drive disease occurrence. This makes sense because the risk of disease will increase if pathogenic bacteria are more likely to be present and/or the farmer does not employ good hygiene practices. That said, different genetic groups exist within breeds, and they strongly vary in their susceptibility to disease. For example, when placed under the same environmental conditions, animals that are more genetically susceptible to mastitis end up with the infection twice as often as do resistant animals. INRA researchers are thus focusing on the genetic basis for disease resistance. They have been looking at the way in which genetics determine a certain number of traits, including disease resistance. This work involves examining the genetic mechanisms involved as well as the breeding methods employed by professionals. The cow is not a model species, and it makes for a difficult experimental subject, given its size, cost, and low reproductive capacity. However, researchers have taken advantage of an enormous database that contains information on a large number of French cattle of different breeds. A total of 40 traits are described, with a focus on productivity, reproduction, longevity, morphology, mastitis infections, and foot diseases. These descriptions have allowed the scientists to estimate an animal's genetic potential and, by considering this information in tandem with data on the animal's genome, to identify the genes involved in shaping a given trait, like disease resistance/susceptibility. For example, a breeding bull is considered to contribute to improved mastitis resistance if his female offspring experience fewer infections than the rest of the female population, all other factors being equal; this means that he has genetically transmitted resistance that he carries to his progeny. By preferentially employing such bulls in breeding programmes, resistance to mastitis can increase in the population at large. However, the information gathered on disease-related traits remains incomplete, which significantly constrains this work. While there is a large amount of data on mastitis, significant efforts are being made to collect more information on other diseases/disease-related issues, such as paratuberculosis, foot diseases, metritis, metabolic diseases, and mortality in young animals.

THE GENETICS UNDERLYING FOOT DISEASES

Foot diseases are one of the main causes for animal discomfort and culling in cattle. However, the influence of genetics on resistance/susceptibility to these diseases remains unclear. INRA has been carrying out a large study exploring this question over the last several years, in which it has been taking advantage of the expertise of hoof trimmers. These "cattle podiatrists" make the rounds of farms to trim and care for the hooves of cows. INRA has recruited these professionals to collect data on 11 different foot diseases. After a training period during which guidelines were discussed and data collection tools were put into place (notably "cow-pie-resistant" tablets), the hoof trimmers got to work. With their help, researchers have created a database that contains information on thousands of animals, including some that have also been genotyped. This database has made it possible to look at relationships between phenotypes and genotypes, to identify differences in genetic potential among animals, and to use the most resistant animals in breeding programmes. Although heritability is very low, around 5%, clear and significant genetic differences have been observed and could be used in breeding efforts. At present, researchers are trying to characterise the genetic variability that determines disease resistance/susceptibility and to understand its underlying causes. This work will not only improve predictions of animal value, which are highly useful to breeders, but will also clarify the factors that trigger disease. For example, the quality of an animal's immune system is not always the trait of greatest importance. Indeed, having a thicker hoof can be enough to reduce the risk of foot diseases.

IMPROVING LIVESTOCK IMMUNOCOMPETENCE AND RESPONSE TO VACCINATION

There is a phenomenon that you are sure to have noticed. During the cold and flu season, certain people never get ill, while others are frequently sick. The same pattern is seen in animals. For example, if we look at piglets raised under the same conditions, some animals will get sick or even die after weaning, whereas others will resist infections or recover more easily if they do get sick. However, because there is currently no way to identify which animals are at greater risk, farmers are apt to preventively treat all of them with antibiotics during the weaning period. INRA researchers have taken on the challenge of identifying the factors that shape animal immune defences. In other words, they wish to determine why certain animals are naturally more disease resistant or respond better to vaccination. To this end, researchers are examining the intestinal microbiota—they hope to observe variations that could help explain these differences in immunocompetence. They are also looking at the genomes of entire populations of pigs, to key in on the genes involved. This work is crucial in efforts to breed animals with stronger health-related traits and to improve the efficacy of vaccines, with a view to reducing antibiotic use. If the factors underlying immunocompetence can be identified, farmers will be able to breed more robust animals that display better responses to vaccines.

DEVELOPING NEW VACCINES FOR LIVESTOCK

For certain diseases in cattle, swine, and poultry, antibiotics are the only solution because effective vaccines are lacking. For example, while a vaccine exists against pathogenic mycoplasmas that infect swine (i.e., *Mycoplasma hyopneumoniae*), it does not work well because of the mutations carried by circulating strains. The situation is worse in cattle: there is no vaccine against *Mycoplasma bovis*. Yet another problem arises in poultry. There is a good vaccine against *Eimeria* species, which cause highly contagious and potentially lethal coccidiosis, but it is too expensive to be used at large scales, like in meat chicken operations. To help provide concrete solutions to these issues, the SAPHIR project (Strengthening Animal Production and Health through Immune Response) was launched as part of the Horizon 2020 Programme. It has brought together researchers from 11 European countries and China. Since 2015, the scientists have been working to develop new vaccines that are cheaper, more effective, and easier to use. They are targeting the six most common livestock pathogens. Also, because some of these potential vaccines are intended to help limit the need for antibiotics, researchers are working with livestock professionals to identify the constraints that hinder vaccine use and the potential ways of overcoming them.

ENDING LAMENESS

Lameness is a problem in meat chickens produced on factory farms. It results in animal discomfort as well as death because afflicted poultry cannot reach the feed troughs. Lameness is primarily caused by *Enterococcus cecorum*, an opportunistic pathogen that is a commensal under normal circumstances (pathobiont). It is known that this bacterium can cross the intestinal epithelium and then infect the vertebrae, leading to lameness. However, further details are lacking. More information may soon be forthcoming: INRA researchers are studying this bacterium with the objective of controlling it. This work is important because, at present, the only way to treat lameness is with antibiotics. Indeed, several treatment cycles are needed, which are given to all the animals, whether they are sick or healthy. Sometimes this approach is for naught because the bacteria develop antibiotic resistance. The researchers' first step was to characterise the diversity that exists in *E. cecorum* strains, with the aim of comparing and contrasting harmless strains with pathogenic strains. They have already sequenced the genomes of more than 100 pathogenic strains and studied their virulence patterns. They will now look at commensal strains isolated from healthy chickens. This research will clarify the specific traits of pathogenic strains and, more importantly, help identify the most virulent among them. The fight against these latter bacteria must be prioritised. Control efforts should involve either vaccines, probiotics (i.e., modifying the microbiota of young chicks), or phage therapy*. However, these approaches will not be enough to completely prevent lameness. For this reason, researchers also want to characterise the antibiotic-resistance genes carried by *E. cecorum*. The result of a collaboration with ANSES, this research will make it possible to precisely determine which antibiotics should be used depending on the strain present. It will also inform treatment regimes—the bacterium should be struck fast and hard given that the goal is to prevent the unnecessary use of antibiotics and to limit the emergence of antibiotic resistance.


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* In phage therapy, bacteriophages (viruses that infect bacteria) are used to treat certain bacterial infections.

ALL UNITED AGAINST MASTITIS

Mastitis and metritis are common inflammatory diseases in ruminants. INRA began a large-scale programme targeting them. Launched in 2013, the three-year multidisciplinary project Ruminflame brought together researchers from 7 scientific divisions and 11 research teams. There were three objectives:

› to improve methods for diagnosing inflammatory diseases in dairy ruminants and to identify risk factors

› to evaluate the effects of nutrition, animal genetics, and epigenetics on inflammatory diseases in dairy ruminants

› to develop alternative methods to antibiotics for dealing with mastitis, including preventive measures like vaccination or the administration of probiotics.


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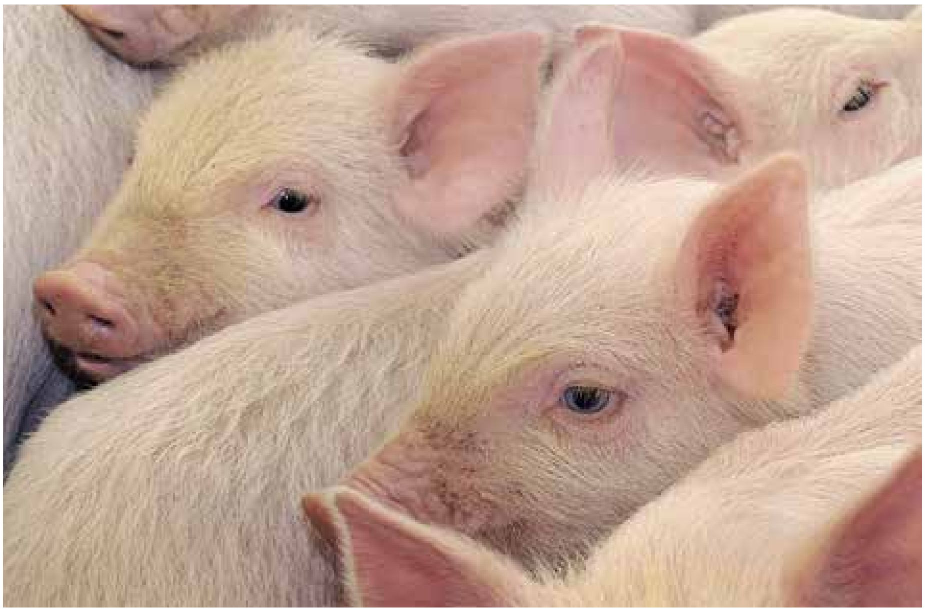
When the first phase of Ruminflame was completed, research continued to be carried out by private-sector partners: a new project, LongHealth, began in early 2018. In the years to come, this work will yield practical solutions for combating these common diseases, which may involve new treatment methods or new recommendations for technical advisors and livestock farmers. For example, researchers have found clear evidence that mastitis causes infertility. Consequently, if greater attention were paid to udder health, it would be possible to avoid the repeated insemination of cows with subclinical mastitis, and thus limit the costs associated with insemination failure, as well as the early culling of animals because of infertility. Accounting for these issues, and implementing other measures, could help improve dairy cow longevity.

BUILDING RESISTANCE

Intra-udder infections are quite common in small ruminants. During a given year, 20–40% of animals develop mastitis. Although the infection remains subclinical most of the time, bacteria are present in the animals' milk, potentially requiring the use of antibiotics. Over the past ten years, INRA geneticists have identified parental lineages that are either more resistant or more susceptible to intra-udder infections. Their work was made easier by the fact that many sheep and goats are described in national databases. The entries include information on animal genealogy, morphology, and milk yield and quality, as well as the results for all the somatic cell counts (SCCs) performed for a given animal. SCCs are a crucial tool for detecting intra-udder infections. Thanks to these data, researchers have been able to build statistical models to quantify the genetic component underlying the resistance of a given reproductive individual, which is used to assign a score. Armed with this information, farmers have been able to selectively breed individuals from the most resistant lineages. As a result, the incidence of mastitis has dropped by about 20% in 10 years. Furthermore, these results are only the beginning, as illustrated by findings from an INRA study carried out on an experimental farm using animals that were highly resistant versus highly susceptible to intra-udder infections. Researchers bred animals in each group with each other. They then raised the offspring in the same place, under controlled environmental conditions. The result was that the female progeny of disease-resistant parents had two-fold lower levels of pathogenic bacteria.

BUILDING TRUST TO STRENGTHEN COMMITMENT



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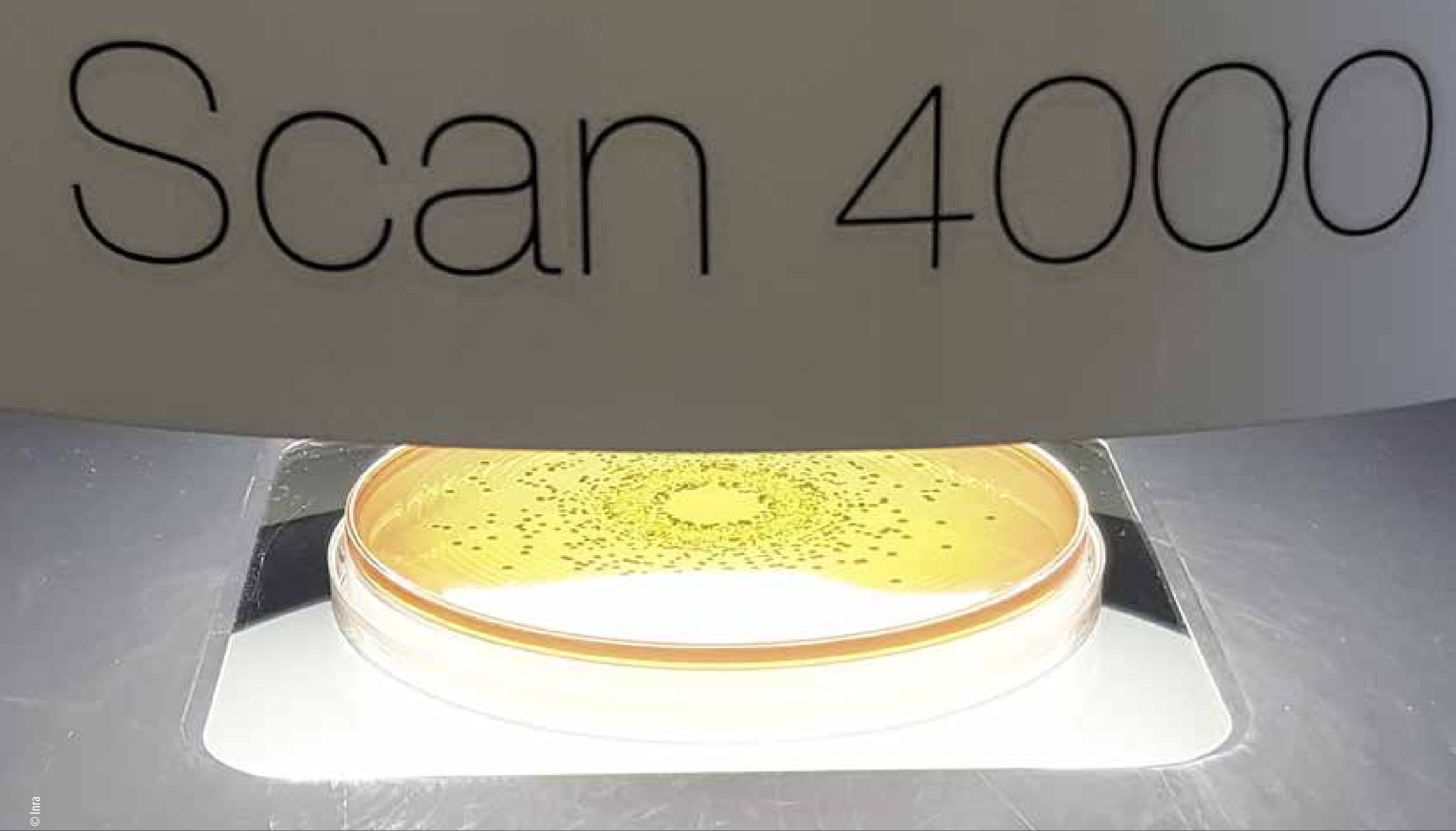
It is indeed possible to markedly reduce antibiotic use in pig operations without necessarily impacting farm technical and economic performance. This discovery was made by the European project Minapig, which ran from 2012 to 2015. Launched at around the same time as Ecoantibio 2017, in which the pig industry was a key participant, Minapig helped identify the main reasons for antibiotic use. As expected, the presence of clinical signs of disease was the main reason for antibiotic use, even when vaccines were available to prevent the occurrence of certain infectious diseases, notably respiratory diseases. The study also showed that establishing a customised action plan, based on an assessment of the animal health situation on the farm, could strongly diminish antibiotic use without affecting production. However, certain farmers remain reluctant to follow the recommendations they have been given, often because they do not believe that the recommendations are in their economic interests or protect animal health. As a result, the Joint Research Unit for Biology, Epidemiology and Risk Analysis in Animal Health (BIOEPAR; INRA and Oniris) initiated the project Prop&Co in 2018. The objective is to change the minds of these hesitant farmers and help others make the transition to more responsible practices. Over the next three years, researchers will evaluate the relationships of 30 pairs of veterinarians and farmers, with a view to determining how relationship quality affects the willingness of farmers to adopt recommended measures for reducing antibiotic use (e.g., vaccination, dietary regimes, hygiene practices). An evaluation grid assessing the farmers' observance of recommendations was created drawing on medical research that was adapted to a veterinary context. The grid was used to characterise and evaluate the factors that help cement trust between veterinarians and farmers. It included categories representing the professional qualities of veterinarians, such as competence, effectiveness, and availability. Also included were categories for personal qualities, such as commitment, kindness, and honesty. Finally, there was a score expressing overall trust, which included the farmer's perception of his or her relationship with the veterinarian. The evaluation grid was used to monitor changes in these relationships over the course of the study. The longer-term goal is to identify the factors that affect trust and the ways in which trust can be improved.

ENGAGING ALL STAKEHOLDERS TO REDUCE ANTIBIOTIC USE

From 2014 to 2018, the project RedAb focused on developing initiatives to limit antibiotic use in dairy cow operations. Working with all the industry's stakeholders, from staff at agricultural high schools to farmers and their advisors, the researchers built a collection of education and training tools focused on methods for reducing the occurrence of mastitis, the disease responsible for the greatest consumption of antibiotics. RedAb researchers performed an experiment. Farmers were assigned to one of two groups. The first group was part of a programme that lasted for more than a year in which farmers could participate in group online training sessions and exchanges. They also individually received customised advice from a technical advisor. The second group was the control group, in which farmers received no training. At the end of the experiment, the results for the two groups were compared. The findings were surprising: antibiotic use dropped in both groups. This discovery shows that, even when stakeholders do not participate in training programmes, awareness is increasing, which serves to change practices throughout the industry.

IMPROVING TRACEABILITY TO LIMIT PREVENTIVE TREATMENTS

How can improving traceability reduce antibiotic use within the whole industry? This question is one of the main lines of investigation in SANT'Innov, a research project focused on veal calves. The reason that this study system was chosen is because the veal calf industry comprises two groups of farmers. There are the calf producers, who raise the beef sucklers until they are weaned, and there are the finishers, who fatten up the animals and then slaughter them. Often, finishers will receive different lots of beef sucklers from different calf producers. This mixing of animals increases the risk that pathogens will be transmitted to the entire herd. In one of the project's studies, it was shown that finishers often do not know the sanitary conditions under which beef sucklers were reared, nor do they necessarily know the number of lots represented by their animals. It is for this reason that certain finishers treat all the animals that they receive with antibiotics, to minimize any infection risks in an effective manner. To reduce antibiotic use by finishers, it will be necessary for calf producers to more systematically vaccinate their animals. The question naturally arises: why are calf producers not doing this already? First, it is difficult and sometimes even dangerous to vaccinate beef sucklers. Second, respiratory diseases often manifest themselves after the calves arrive at the finishers. To help reduce the preventive deployment of antibiotics, researchers sought to increase the involvement of all stakeholders. To this end, they worked with a co-op to create a risk analysis grid that can describe lots of calves and improve traceability. With access to this information, finishers can choose to only accept vaccinated lots of animals or will at least be able to exclusively treat at-risk animals. While the grid still needs some work, it can already correctly classify 70% of lots.



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FINDING ALTERNATIVES

The preventive use of antibiotics significantly contributes to the spread of antibiotic-resistance genes. The problem is that, in certain situations, farmers risk losing livestock. They therefore feel compelled to treat all their animals to prevent a sick individual from infecting the others. However, it may soon become possible to offer farmers other solutions. For example, research on the microbiota has identified bacteria that could be employed as probiotics to effectively fight certain infections at key moments of an animal's life. INRA researchers are also assessing the ability of essential oils and algae to stimulate immune defences and prevent certain diseases.

EXPLORING THE VIRTUES OF ESSENTIAL OILS

Could essential oils (EOs) be used to treat and/or prevent mastitis, metritis, and certain respiratory diseases in dairy cows? Certain farmers believe so and have been using them to medicate their animals for years. Most, however, would like to have evidence of their effectiveness first. Some are already using them but have obtained mixed results, while others are not ready to commit. Assessing whether or not aromatherapy is beneficial for animals is an important task. While EOs have been shown to have benefits in humans, they should be used with care. Indeed, they can cause harm if used improperly or at overly high doses. A team of INRA researchers is currently carefully evaluating the effectiveness of this substances. For the moment, they are carrying out *in vitro* experiments in the laboratory to clarify the influence of EOs on the mechanistic causes of inflammation provoked by bacterial pathogens. The focus is currently on EO active compounds, which are being analysed individually. In general, an EO contains at least four or five active compounds, and a large number of these compounds are found in numerous oils. However, effectiveness may vary among mixtures. Consequently, researchers will be testing combinations of active compounds, like the ones found in commercialised EOs. Is it therefore possible that aromatherapy could help reduce antibiotic use? It is still too early to tell for sure, but the researchers say that EOs, used preventively or following the first signs of infection, could help activate and stimulate host immune defences. They could also be used in tandem with antibiotics, to optimise their effects. These hypotheses remain to be confirmed by future *in vivo* experiments.

REDUCING STRESS IN MEAT CHICKENS VIA ESSENTIAL OILS

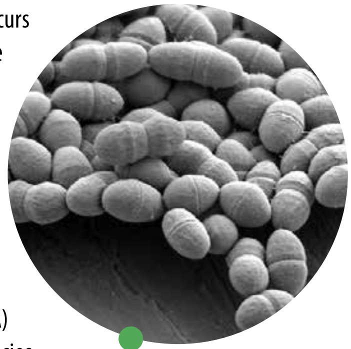
Upon hatching, meat chicks are transferred from the hatchery to the grow-out facility; some neither eat nor drink for three days. The stress and deprivation experienced by these animals can lead to greater fragility and lower performance, in comparison to animals that do not experience such conditions. At the scale of the whole farm, the consequences can be significant. Researchers studied stress and self-medicating behaviour in meat chickens. In the experiment, there were two groups: one containing control chicks and another in which chicks experienced stressful conditions (simulating those described above) for a 24-hour period. The groups were then both raised in chicken runs containing two watering troughs whose position was changed every day. One trough contained water. The other contained either water or water plus an EO containing verbena, cardamom, or marjoram. Both troughs were accessible to the chicks at all times. The aim was to determine the effect, if any, of EOs on chicken performance, notably weight gain and muscle acquisition. The study showed that, compared to the control chickens, the treatment chickens consumed more of the verbena EO, which is known to have a soothing effect, reduce inflammation, and improve digestion. The marjoram EO was also consumed but to a lesser degree. Finally, the chicks consumed virtually none of the cardamom EO, even though it has anti-oxidant, anti-inflammatory, and anti-spasmodic properties. According to the researchers, this behaviour could be explained by the fact that chickens can spontaneously consume different types of plants, depending on their state of health: in essence, they can self-medicate. Although the intake of EOs did not allow the treatment chickens to regain the weight that they had initially lost, they were able to rebuild their muscle mass, especially in the breast area. These results could help convince farmers to add EO watering troughs alongside normal watering troughs. While some farmers already add EOs to their poultry's food, to increase their performance, the researchers feel that this systematic approach is not ideal. This work shows that it is better to allow chickens to consume the EOs that improve their state of health at a given moment.

WHAT IF THE MICROBIOTA COULD TREAT MASTITIS?

Mastitis is the most common disease experienced by dairy cows. It is an inflammation of the udder and is often caused by bacterial infections. Most farms experience economic losses due to mastitis. Since there is no effective vaccine for this disease, farmers treat mastitis with antibiotics, an approach that is not always successful. However, new solutions are being developed that could prevent cows from becoming infected; mastitis is both painful to animals and stressful for farmers. Over the past several years, INRA researchers have been characterising the microbiota of dairy cow teats. Several questions have arisen: Does microbiota composition play a role in the infection process? Do cows that rarely get mastitis have bacteria that help protect them? If so, which bacteria? Is it possible to modify the microbiota to reduce infection risks? *In vitro* experiments have shown that the answer to at least some of these questions is "Yes". For example, researchers discovered that the bacterium *Lactobacillus casei* hinders the ability of *Staphylococcus aureus* to turn pathogenic. This latter bacterium is one of the main species responsible for mastitis. *In vivo* experiments are necessary to confirm this mechanism. However, if they do, it could be possible to develop a probiotic aimed at strengthening the microbiota of dairy cows. A diagnostic tool could be used in tandem to help farmers rapidly identify animals whose microbiota promote the development of mastitis. By managing the herd's health at a very fine scale, farmers could then act rapidly, as soon as the first signs of disease appear. However, researchers would like to go even further and envision administering mixtures of beneficial bacteria to young animals, with a view to shaping their microbiota and, notably, improving their resistance to pathogens. In extreme cases, it may even be possible to carry out teat microbiota transplants, as is already done in humans with the intestinal microbiota.

BACTERIA THAT GO BIG

Have you heard of pathobionts? They are commensal bacteria* in the intestinal microbiota that can become opportunistic pathogens. Under normal circumstances, they are unremarkable. They are far less numerous than other commensal bacteria. However, if given the opportunity, they can turn dangerous. If they are normally rare, it is mostly because other bacteria consistently and strongly control their numbers via competitive pressure, which means that such bacteria are clearly beneficial. However, in the absence of competitive pressure, pathobionts can multiply rapidly, especially when a host's immune system is weak. They can then overwhelm the host's defences and become pathogenic. *Enterococcus faecalis* is a commensal bacterium that occurs in the digestive tract. It is a pathobiont and can cause fatal nosocomial infections. What happens is that the intensive use of antibiotics or anti-cancer drugs leads to imbalance (dysbiosis) in the intestinal microbiota, creating conditions that are ripe for the development of *E. faecalis*. This bacterium is resistant to several antibiotics, but antibiotics remain the main method for eliminating it. INRA researchers are working to help prevent such situations. But how? They are looking for bacterial members of the microbiota that can stop or at least limit the growth of *E. faecalis* within the intestine. To this end, researchers conducted an experiment in which mice were treated with antibiotics to generate dysbiosis and cause the overdevelopment of *E. faecalis*. They then stopped the treatment and observed how quickly the intestinal microbiota returned to normal and how long it took for the intestinal microbiota to naturally force the pathobiont back down to its usual low levels of abundance. In collaboration with mathematicians in the Applied Mathematics and Informatics (MIA) Division, who modelled the changes in the microbiota, the researchers managed to identify several of the bacterial species that mediate this process, which may serve to antagonistically control *E. faecalis*. The next step will be to identify equivalently beneficial bacteria in humans. The ultimate goal is to use such bacteria as probiotics that could be given to a patient in tandem with antibiotics. It could thus be possible to prevent dysbiosis and the overdevelopment of *E. faecalis*. The model developed for this system could also be helpful for studying other opportunistic pathogens, including *Klebsiella pneumoniae*, a commensal enterobacterium that is particularly resistant to antibiotics and that also causes fatal nosocomial infections.



Enterococcus faecalis, a commensal bacterium in the digestive tract and an opportunistic pathogen.
© Inra - Lionel Rigottier-Gois & Thierry Meylheuc

* A commensal bacterium is a bacterium that lives in its host without causing harm.

FARMERS SEEKING ALTERNATIVES TO ANTIBIOTICS

It is clear that researchers are dedicated to finding ways to reduce antibiotic use in the livestock industry. However, they are not alone. A growing number of farmers are also trying out alternative methods for treating animals, such as EOs, herbal medicine, homeopathy, or special dietary regimes developed by private companies. What are the reasons for this trend? This is the question being asked by INRA sociologists, who are traveling all over France to interview farmers who are seeking to reduce their dependence on antibiotics. The results seem to indicate that there are multiple reasons for this trend. From an economic perspective, these alternative solutions are less expensive than antibiotics or vaccines. However, the health and well-being of their animals remain the farmers' main concern. Additionally, farmers are worried that certain antibiotics will become unusable (the ones they employ, which could be rendered ineffective by excessive usage). They do not want to find themselves empty handed when facing livestock infections in the future. The sociologists wish to understand how innovative practices are emerging in the field and to identify the network of stakeholders responsible for disseminating these new methods. The scientists are also creating a list of the methods and techniques that could be evaluated by researchers specialising in animal health. While some research on the effectiveness of EOs is already underway at INRA, other practices likely deserve to be studied in detail as well.

SIMULATING CONDITIONS IN THE PIG COLON

Weaning is an important period in a pig's life. The dietary and environmental changes that take place induce stress, increasing the likelihood of infections. This issue is particularly important in intensive farming systems, where piglets are weaned much earlier than would occur naturally. Because their digestive and immune systems are still immature, they are especially susceptible to highly contagious and sometimes lethal *E. coli* infections. Because no effective vaccine is available, antibiotics are the only way to prevent the disease from spreading among livestock once it has appeared on a farm. Given the economic costs of these infections, some farmers continue to preventively treat all piglets with antibiotics, which goes against Ecoantibio recommendations. However, this situation may be changing. Over the last several years, a team of researchers from INRA and the University of Clermont-Auvergne has been developing a study system for characterising the effectiveness of alternative methods for controlling these pathogens. They are using a bioreactor, a device that can simulate conditions within the piglet colon. They can thus recreate the animal's microbiota and observe how it reacts to the stress induced by weaning and infection. This system can even be used to study the transfer of antibiotic-resistance genes between the commensal flora of the colon and bacteria in the external environment. Researchers can cause dysbiosis in the microbiota—simulating the stress experienced by piglets during weaning—and then introduce prebiotics or probiotics to determine the effects on the microbiota and pathogens. The development of this study system is still underway; the private company Lallemand Nutrition Animale has provided doctoral funding via CIFRE, a French industrial convention for research-based training. In one or two years, this study will have yielded recommendations for alternative treatments, such as which probiotic strain should be used for a given bacterial pathogen; the optimal dose of probiotics needed to be effective; or the circumstances in which prebiotics and probiotics should be combined to take advantage of their synergistic reactions. The idea is to apply such treatments during the weaning period, to help limit dysbiosis, stop infections, and restore balance to the microbiota.

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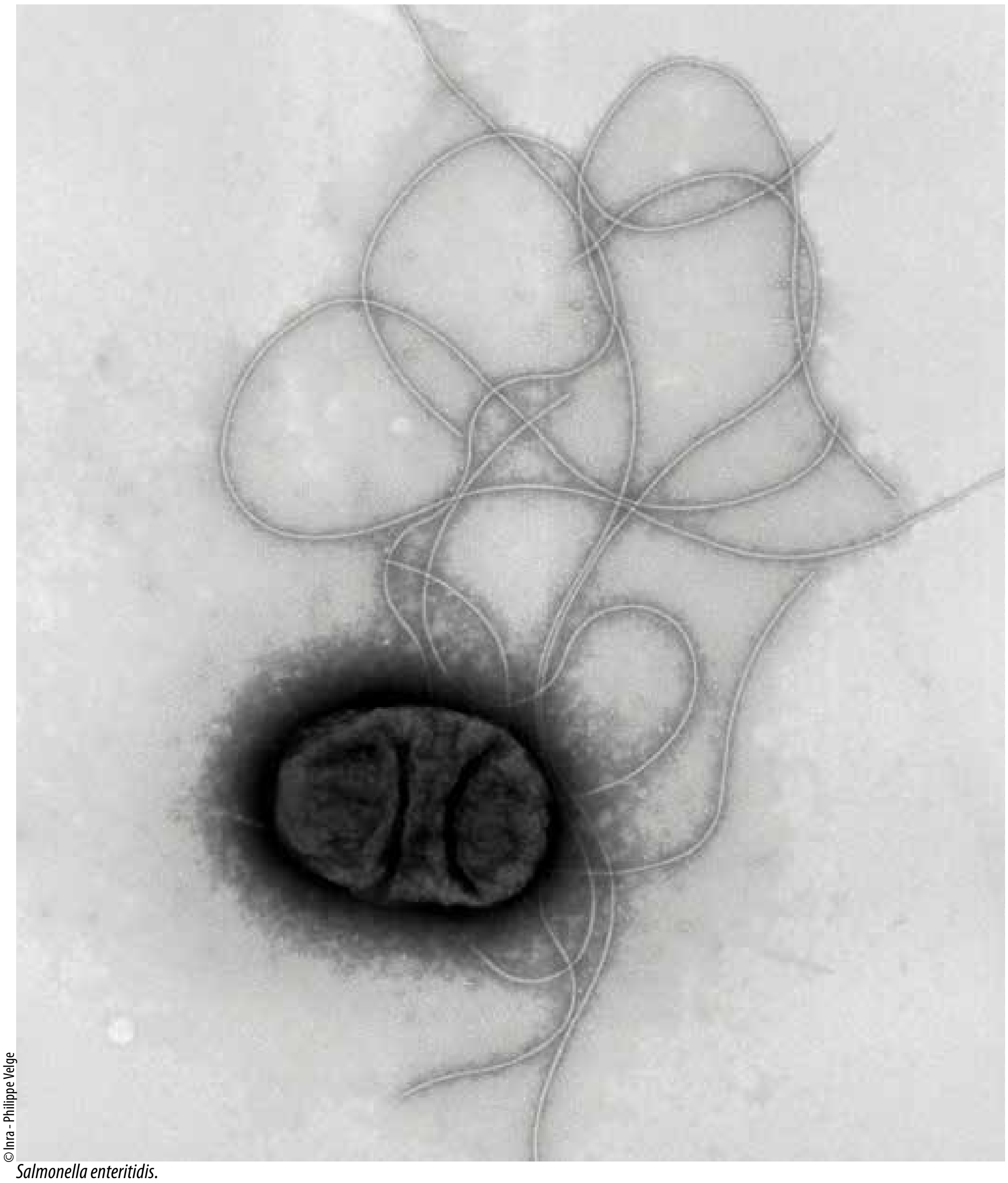
ARE YOU VULNERABLE OR RESISTANT TO SALMONELLA BACTERIA? CHECK YOUR MICROBIOTA

Here is a perfect One Health challenge. Salmonellosis is a potentially lethal bacterial infection. Humans become sick after consuming contaminated food, notably eggs, chicken, or pork. However, except in rare cases, the animals responsible for passing along the bacteria do not display signs of sickness. They are thus asymptomatic carriers. Consequently, to limit the risks of food contamination and transmission to humans, it is important to deal with infected animals. Until recently, it was thought that certain poultry lineages were more or less resistant to salmonella bacteria, displaying what is termed host genetic resistance. However, an INRA research team showed that there is dramatic variability within lineages. Indeed, some animals from a given lineage are super shedders—they are extremely susceptible to infection by salmonella bacteria and develop highly contagious infections (i.e., their faecal matter is loaded with bacteria). In contrast, others from the same lineage are much better at resisting initial infections. Recently, the researchers demonstrated that susceptibility/resistance is tied to the pre-infection composition of the intestinal microbiota. As part of a European research project, the scientists are now trying to develop a system for identifying the most susceptible chicks by analysing their microbiota. They will also design quick and easy tools for testing animals, so that farmers can be aware of infection risks as early as possible. Most importantly, the researchers want to determine which members of the microbiota prevent colonisation by salmonella bacteria. The goal over the longer term is to develop probiotics that could be given to susceptible animals immediately after hatching to increase their resistance.



Salmonella enteritidis.


© Olmix - L. Rannou

ALGAE: AN INEXHAUSTABLE SOURCE OF WELL-BEING?

Although it still surprises tourists, the sight of the algae harvest is now commonplace for those living along France's Atlantic Coast. At low tide, odd-looking harvesting equipment combs entire tidal flats to collect green and red algae. The cell walls of these photosynthetic organisms contain large quantities of sulfated polysaccharides—sugars with anti-parasitic and anti-viral properties that can also modulate the immune system. Olmix is a French company that was created in 1995. It makes commercial products from algae, namely food supplements for humans and animals. In 2013, Olmix began working with INRA to evaluate the effectiveness of a marine-sulfated polysaccharide (MSP) extract obtained from *Ulva armoricana*, a type of green algae harvested in Brittany. Researchers experimentally tested the effects of these sugars on 42 strains of pathogenic bacteria representing the most common agents of infection in cattle, swine, and poultry. In all cases, bacterial development was negatively impacted. The magnitude of the effect depended on the strain. The researchers also found that the sugars stimulated pig intestinal epithelial cells to produce immune mediators, indicating that MSPs may act by stimulating intestinal immunity. The MSPs contained in marine algae could thus be incorporated into the diets of livestock to inhibit the growth of pathogenic bacteria within the digestive system and to stimulate immune responses. This approach could improve the robustness of animals at risk of infection and help reduce antibiotic use in livestock in general. In the short and intermediate term, INRA and Olmix want to verify these results *in vivo* by carrying out studies in which target species are experimentally infected with pathogens. The longer-term objective is to obtain natural compounds with scientifically demonstrated infection-fighting properties that can be added to livestock diets. The desired effect is to preserve animal health and intestinal well-being. This supplementary approach could help prevent infections and thus limit antibiotic use.


© Olmix - Hervé Cohonner

Streptomyces ambofaciens colonies.
© Inra - Pierre Leblond

THE HUNT FOR NEW TREATMENTS

Ciprofloxacin has just turned 30. Since its creation, no new antibiotics have been commercially developed. However, this does not mean that research has stopped. INRA researchers are hunting for new compounds that could be added to the treatment arsenal, whose size has shrunk as a result of antibiotic resistance. They are also investigating new, ambitious control methods, such as the development of medicines that target individual bacterial species; techniques for disarming pathogens and encouraging their elimination by the immune system; and treatments that exploit "quorum quenching".

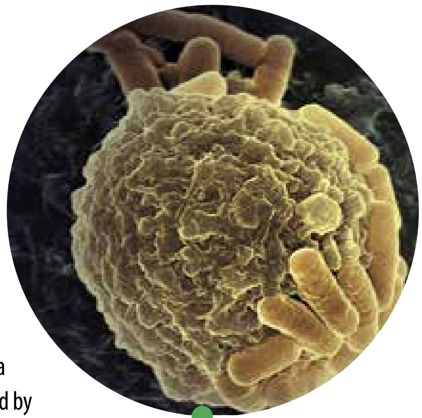
ON THE TRAIL OF NEW COMPOUNDS

Consider a handful of soil taken from a forest, field, or grassland. While it is not visible to the naked eye, tremendous biodiversity lies in the palm of your hand: the soil is replete with mites and other arthropods as well as hundreds of nematodes, thousands of fungi, and millions of bacteria, including *Streptomyces* species. These bacteria produce compounds that have been used for decades because of their anti-bacterial, anti-fungal, and anti-tumoral properties. For example, streptomycin is an antibiotic that was discovered in 1943. It is produced by the bacterium *Streptomyces griseus*. However, until recently, researchers had only been able to isolate a small number of active compounds from a single *Streptomyces* species. This state of affairs has changed thanks to recent advances in genomics. Scientists have discovered that these bacteria have 20 to 40 genes or gene groups that potentially encode active compounds. There is even more good news. While *Streptomyces* species share a small number of these genes, they also each carry unique genes, which increases the potential diversity of such compounds. Indeed, this diversity is such that, with each new isolate, researchers discover new genes. Around 600 species of *Streptomyces* have been identified to date, but there are likely to be many more. This research is already bearing fruit—researchers at INRA and the University of Lorraine have identified a new compound in the macrolide class of antibiotics that displays anti-tumoral activity.

THE SECRET LIFE OF BACTERIA

Imagine that you take a lion, place it in a cage, and study its behaviour. Although the experience may be interesting, you will not learn much about the lion's natural habits, diet, or abiotic/biotic interactions. In contrast, observe the lion in its normal habitat, the savannah. Its behaviour will be entirely different. It will engage in interactions with other lions and be forced to hunt for food. The same is true for bacteria. At present, most bacteria are studied individually in the form of cultures grown in Petri dishes. Because they are not interacting with other organisms, as they would in their natural environment, they express just a small number of the genes they carry. As part of a doctoral project that begin in 2017, INRA researchers will attempt to identify novel compounds by recreating microbial interactions. To this end, they will put bacteria and fungi together and observe the results. Researchers expect to see the micro-organisms express various compounds that could be of interest for human and animal health.

NEXT-GENERATION ANTIBIOTICS?



Bacillus cereus.
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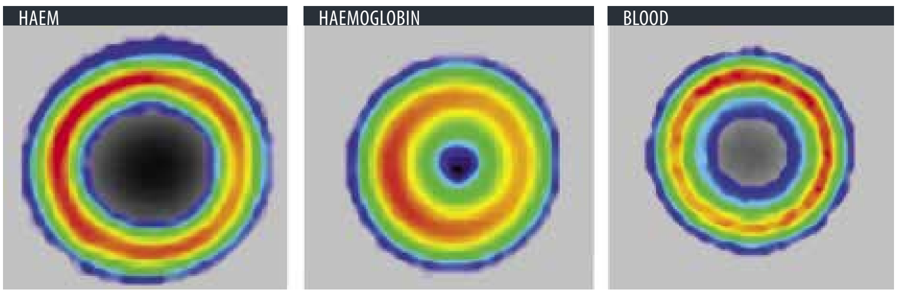
Antibiotics are indiscriminate assassins. They target the survival mechanisms shared by all bacteria. As a result, when they are used to treat infections, they will eliminate pathogenic bacteria, as intended, but they will also kill off symbiotic bacteria in the microbiota. As we have seen, one result is dysbiosis. Another is the emergence of resistance, including in commensal species. However, an INRA research team may have found a way to avoid such wholesale slaughter, thanks to a new mechanism of antibiotic action. When humans are infected by a bacterium, their bodies deploy an array of immune defences to fight the invader. Ironically, the bacterium becomes pathogenic because of the effects of the proteins it produces to defend itself. The researchers came up with a way to inactivate these proteins, which essentially strips the bacterium of its defences. This approach is novel because, for the first time, the antibiotic is not intended to kill the bacterium. Instead, the goal is to help the immune system do its work. Adopting this tactic has an additional benefit: because it targets proteins that function in the infection process, it will not harm commensal bacteria. Indeed, commensal bacteria are not targeted by the host's immune system and therefore have no reason to express these proteins. Furthermore, these proteins are not essential to their survival. Furthermore, the use of this antibiotic will not have an effect if it is administered preventively, which will help limit the risks of antibiotic resistance emerging after metaphylaxis. Researchers have already identified one source of protein production and have developed several compounds that can target the proteins. During *in vitro* tests, one of these compounds was able to effectively disarm several pathogenic bacterial species, including some that display high levels of antibiotic resistance. The next step is to determine if these results can be replicated *in vivo*. Researchers will start off by using insects in order to reduce the experimental use of mammals as much as possible.

A LOVE-HATE RELATIONSHIP WITH HAEM

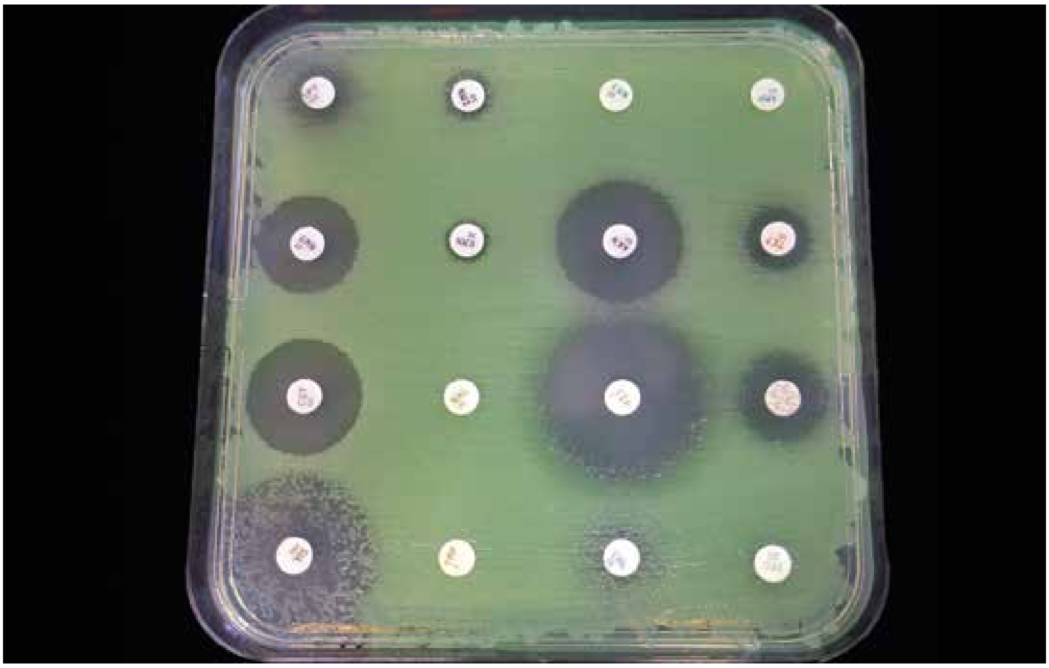


Bioluminescent bacteria with a haem sensor.
© Inra

In animals, oxygen transport is carried out by haemoglobin, the protein that gives blood its red colour. The work is actually performed by haem, the compound embedded within the haemoglobin's subunits. An iron atom is found at the centre of the haem molecule. Iron is an essential nutrient for certain Gram-positive bacteria, such as *Streptococcus agalactiae* and *Staphylococcus aureus*. Indeed, their virulence depends on it. However, harvesting iron is not always easy because excessive levels of haem are very toxic. To avoid haem poisoning, certain bacteria have developed a very clever technique. For example, *S. agalactiae* has a haem sensor, which sounds the alarm when the molecule is detected nearby. The bacterium then expresses an efflux membrane transporter, which directs excess haem out of the cell and into the environment. This action is similar to ships pumping out water that has flooded the hold. The bacterium can then safely degrade the remaining haem to access the iron. An INRA research team has shown that bacteria that have lost the ability to express this pump (i.e., mutants) cannot escape the toxicity of the host's blood. They die before being able to cause an infection. Researchers are now untangling the mechanism used by the sensor to detect haem with the goal of inhibiting its function and thus blocking the bacterium from becoming virulent. Because these sensors vary among species, this work could uncover new compounds that can more precisely target pathogens, such as *S. aureus*, and thus put an end to the collateral damage to commensals. Furthermore, when infections occur, such compounds could be used in tandem with antibiotics, increasing treatment efficacy.

CUTTING OFF COMMUNICATION

Bacteria possess a mechanism called quorum sensing, which is used by pathogenic bacteria to enhance virulence. When they encounter favourable environmental conditions, they start producing signalling molecules, which they release into the extra-cellular environment. These molecules announce the bacteria's presence to conspecifics. As the bacterial population grows, the quantities of signalling molecules increase as well. When the threshold value, or quorum, is reached, all the members of the population simultaneously express their toxin-encoding virulence genes, which leads to infection in the host. This mechanism, almost militaristic in its implementation, has drawn the attention of researchers. For the past several years, scientists have been exploring methods for interrupting communication among bacteria (i.e., quorum quenching) as a way to inhibit the expression of virulence genes. These methods include inhibiting the synthesis of the signalling molecule; promoting its degradation once it has been secreted; or blocking the molecule's reception by bacteria. In all three cases, the focus is on interfering with the bacterium's attack rather than on killing the pathogen outright. Researchers have spent several years testing this approach with plant pathogens, and the results are promising. Furthermore, the signalling molecule was successfully inhibited in research utilising cutaneous infections in mice. However, when it comes to dealing with infections in internal organs, such as the lungs or the respiratory tract, the task becomes more complex. To be successful, inhibitory agents must arrive at the infection site without being intercepted by the immune system. It is worth investing in this challenging research since quorum quenching represents a promising alternative solution to antibiotic use. Moreover, by targeting the signalling molecules rather than the bacterium itself, there is a significantly reduced risk that antibiotic resistance will emerge.



An antibiotic susceptibility test (bacterium: *Pseudomonas aeruginosa*).

A SHOW IN THREE ACTS

A VERY OPPORTUNISTIC BACTERIUM

Thirty years! It is hard to believe, but the last major family of antibiotics arrived on the scene in 1987. All of its members are now facing various levels of bacterial resistance. It is also important to note that, in 2006, Merck announced it had discovered a new drug that could be used in the fight against Gram-positive bacteria. This news was greeted with enthusiasm. In an article published in *Nature*, researchers in the US announced that they had successfully blocked the fatty acid synthesis pathway in streptococci and staphylococci. Fatty acids are essential components of phospholipids. The pathway was thought to be necessary for survival because phospholipids are crucial in the construction of the bacterial membrane. A celebration was seemingly in order, except that the situation was not so simple. At that time, INRA researchers studying *Streptococcus agalactiae* observed that this pathogenic bacterium could build its membrane using fatty acids from the environment. It could also use fatty acids it had gathered from its host. It was thus clear that the bacterium had no need to manufacture the building blocks of its membrane, an ability that results in significant energy savings. The researchers published this work in 2009, also in *Nature*.

STAPHYLOCOCCUS AUREUS: NO STRESS, NO PROBLEM

This was not the end of the story. Although the new antibiotic was not effective against streptococci, it was thought that it could potentially work quite well against staphylococci (i.e., *Staphylococcus aureus*). At least, that was the opinion of certain scientists and representatives of pharmaceutical start-ups who claimed that this bacterium synthesised a unique and indispensable fatty acid that could not be found in the environment. In such a case, could blocking fatty acid synthesis be effective? Yet again, the situation was not so simple, as INRA researchers demonstrated. They showed that the bacterium had a hard time using fatty acids harvested from the environment when experiencing stress. In such situations, it was at least somewhat susceptible to the antibiotic. However, in the absence of stress, the bacterium could still use environmental fatty acids to build its membrane, just like streptococcal species. This result indicates that, under non-stressful conditions, it could escape the antibiotic's effects.

AN ANTIBIOTIC ONE-TWO PUNCH

In that case, why not subject the bacterium to a stressor, to make it more vulnerable to the antibiotic? Such is the goal of research currently being carried out at INRA. The results thus far are promising. Using *in vitro* tests, scientists induced stress in *S. aureus*, interfering with its ability to gather fatty acids from the environment. Another approach is also being studied: blocking the bacterium's ability to use fatty acids of environmental origin and thus interfering with membrane building in non-stressed bacteria. Again, the results thus far are encouraging. The objective is to combine the two strategies in a single treatment, by cutting off the supply of external fatty acids and preventing the synthesis of fatty acids "in-house". The first *in vivo* tests will begin in 2019.

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ANTIBIOTIC RESISTANCE: UNIFIED ACTION FOR A SHARED PROBLEM

R2A2, A THINK TANK ON ANTIBIOTIC RESISTANCE

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UNDERSTANDING RESISTANCE MECHANISMS

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ANTIBIOTICS: PREVENTIVE TREATMENTS ARE NOT ALWAYS HEALTHY

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ALL UNITED AGAINST MASTITIS

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