Inserm

La science pour la santé
From science to health

Key points of the **French national Priority Research Programme on**

Antibiotic resistance

"Research today, means reducing antibiotic resistance tomorrow"

GOUVERNEMENT
Liberté
Égalité
Fraternité

LE GRAND PLAN D'INVESTISSEMENT

ANR

At the initiative of the General Secretariat for Investment and the French Ministry of Higher Education, Research and Innovation, the ***French national Priority Research Programme*** **(Programme prioritaire de recherche - PPR)** *on antibiotic resistance is funded with an investment of* ***40 million euros*** *over 10 years, within the framework of the third Governmental Investments for the Future programme* (Programme d'investissements d'avenir - PIA3).

Its main objectives are to ***implement*** *an ambitious research programme by bringing together national research players, and* ***propose*** *new public health strategies and control measures to reduce and optimise antibiotic use in human and veterinary medicine. The ultimate goal is to reverse the resistance curve, in line with international actions.*

The national institute for health and medical research (Inserm) has been entrusted with the scientific steering and coordination of this research programme. The French National Research Agency (ANR) is the programme operator.

"One Health"

The "One Health" approach conceptualises human, animal and environmental health as one, integrated system. As dissemination of resistant bacteria between humans, animals and the environment is a key factor in the spread of antibiotic resistance, it is essential to develop control strategies that do not dissociate humans from their environment. This underlines the urgent need to support a holistic research response to challenges in these three sectors.

Problematic and consequences of antibiotic resistance

Antimicrobial resistance is a global phenomenon with no geographical or species boundaries, which poses an important threat to human, animal and environmental health. It is a complex and growing problem that compromises our ability to treat bacterial infections.

All areas of medicine involving a risk of infection are affected, including surgery, onco-haematology or organ transplantation. In several disciplines, medical practitioners are already confronted with patients at a therapeutic dead-end.

Antibiotics

Antibiotics, molecules capable of killing or inhibiting the growth of bacteria, represent one of the most important discoveries in medicine. They have saved millions of lives since the 1940s. However, their wide-spread or inappropriate use has led to numerous problems, the most important being the emergence of bacteria resistant to antibiotic treatment.

If no prompt action is taken, infectious diseases of microbial origin could cause more than 2.4 million deaths in Europe, North America and Australia over the next 30 years[1].

In response to this urgent global challenge and in agreement with the Word Health Organisation (WHO) recommendations[2], France has joined other European countries and the USA, in launching a national Priority research programme focused on antibiotic resistance[3]. These initiatives outline the major national research priorities and objectives for the next 10 years, constituting an essential framework to foster more coordinated nation-wide research efforts and improve international collaboration and capacities.

In France, 139,105 infections in healthcare institutions have been attributed to multi-resistant bacteria in 2016, resulting in a substantial financial burden for the national public health insurance (estimated at M€100 for 2015)[4-5].

Antibiotic resistance is not specific to bacteria responsible for infectious diseases. Scientific evidence suggests that the microbiome – a collection of non-pathogenic bacteria, viruses, parasites, fungi and their genetic material – represents a reservoir and potential source of resistant bacteria that can enhance dissemination.

To fully understand the problem of emergence, transmission and spread of antibiotic resistance, broader factors must also be considered including misuse and unintended exposure to antibiotics, resistant bacteria and resistance genes in humans, animals and the environment.

Implementation of the French national Priority Research Programme (PPR) on antibiotic resistance

The PPR on antibiotic resistance focuses on the following priorities: explore new strategies to reduce antibiotic resistance, open new avenues of research, respond to the need for alternatives to antibiotics, and give rise to an important behavioural shift in healthcare professionals and the general public in regards to appropriate use and exposure to antibiotics.

In response to these challenges, the plan is developed around four inter-disciplinary and interconnected pillars within the "One Health" context.

[1] OECD (2018), Stemming the Superbug Tide: Just A Few Dollars More, *OECD Health Policy Studies,* Éditions OCDE, Paris. https://doi.org/10.1787/9789264307599-en

[2] WHO (2015), Global action plan on antimicrobial resistance. *World Health Organization,* https://apps.who.int/iris/handle/10665/193736

[3] Jouvin-Marche et al. French research strategy to tackle antimicrobial resistance. *The Lancet.* 2020. https://doi.org/10.1016/S0140-6736(20)30477-3

[4] Opatowski et al. *Epidemiol Infect.* 2019; 147:e144

[5] Touat et al. *Appl Health Econ Health Policy.* 2019; 17(3):381-389

Key outcomes supported by the national antibiotic resistance programme

- Identify the underlying mechanisms that enable bacteria to resist to antibiotic treatment in humans and animals.
- Understand the asymptomatic carriage of pathogenic bacteria in humans and animals and elucidate why some patients, at high risk of infection during hospitalisation, are not infected.
- Explore host mechanisms (immune, genetic, nutritional, psychological) that determine susceptibility to bacterial infection, in order to propose more effective therapeutic treatments and avoid the emergence of new resistance.
- Study the biology of bacteria to identify novel therapeutic targets and understand mechanisms through which multidrug resistant bacteria emerge, resist to their environment and treatments, replicate, persist via reservoirs and spread in different organisms and the environment.
- Develop new detection and early diagnostic tools to control, as early as possible, bacterial colonisation of the host and the population (human and animal). The objective is to delay possible epidemics and control all reservoirs.
- To analyse and understand the perception of the risk of antibiotic resistance and raise awareness of all health professionals and consumers on the responsible use of antibiotics.

Facing four scientific challenges by funding ambitious interdisciplinary projects and infrastructure

Interdisciplinarity is key to reaching the aforementioned outcomes. It is crucial to bring together scientists from different backgrounds and engage disciplines that have not yet prioritised antibiotic resistance. Such an approach will allow the combination of skills and expertise to explore new research avenues and meet the need for innovation, alternative strategies, technological breakthroughs and incite fundamental behavioural changes in the healthcare setting and members of the public leading to appropriate use of antibiotics.

In response to calls for interest published by the ANR, researchers will be invited to propose projects in the form of letters of intent, based on the priorities established by the PPR. Consortia will be formed following each call for interest. Calls for interdisciplinary projects are being launched in 2020 and will be evaluated by an international committee.

The first call for interests "Antibiotic resistance: understand, innovate, act" includes 4 challenges:

- **Dynamics and control of the emergence, transmission and spread of resistance**

  We are facing a global dissemination of antibiotic resistance. Taking action against this affliction requires studying the mechanisms of emergence, transmission and spread of antibiotic resistance, including in the environment, animal and human ecosystems, using a combination of mechanistic and novel information-based technology approaches. The ultimate objective is to model processes in order to assess and predict the level of risk of acquisition, transmission and spread of antibiotic resistance.

- **Optimising the use of antibiotics in human and veterinary medicine**

  Improving the use of antibiotics requires the development of tools and strategies that optimise the effectiveness of antibiotics while limiting their undesirable consequences, from the clinical, epidemiological, economic and environmental points of view. The development of such diagnostic, modelling, data mining and deep learning tools are core axes of this challenge.

- **Individual, ethnological and sociological, economic, political and cultural determinants of antibiotic resistance**

  It is important to improve our understanding of decision-making processes underlying antibiotic use and to identify environments and mechanisms that improve prescription and usage. It is also necessary to analyse and identify ways to promote hygiene and minimise the release of antibiotics into the environment. This requires analysing, understanding and characterising contextual determinants and social factors, identifying economic logics, individual or professional practices, legal frameworks, dialogues, situations, observing population groups, social, institutional and private actors, and locations for decision-making and communication of the problematic. The objective is to identify the social and economic impacts of these behaviours and practices, as well as their consequences.

- **Therapeutic innovation**

  New therapeutic and preventive strategies must be considered to counter the development of antibiotic resistance through a holistic approach that integrates environmental considerations, animal contexts and human health. This scientific challenge aims to identify and develop innovative therapeutic and preventive alternatives that respect commensal flora and non-targeted bacterial ecosystems. The identification of new molecules, the repositioning or combination of existing molecules, immunotherapy, phage therapy or faecal transfer are at the heart of this challenge. If necessary, all these strategies can be combined with modelling and artificial intelligence approaches.

Combining skills and expertise through professorships

Interdisciplinary junior and senior professorships will be funded to strengthen consortia of research scientists and selected research projects. In this framework, priority will be given to recruiting researchers with dual expertise (e.g. biology and medicine, biology and digital sciences, social sciences and biology/health… A national call will be organised by the ANR in consultation with academic research institutions and universities concerned with antibiotic resistance.

Implementation of tools

The national research programme will fund essential tools to meet the research challenges at hand:

- **Creation of an integrated microbial and multi-omics data platform**

The platform will be dedicated to antibiotic resistance, take into account the interoperability of biobanks and databases, and include the development of mathematical and bioinformatic tools. This platform will facilitate modelling of the evolution and spread of resistance, and evaluate the impact of the interventions.

- **Integration of health databases**

Health databases are essential to integrate patient's data from all healthcare settings and the environment. This will require development of specific software and artificial intelligence in collaboration with the Health Data Hub currently under development.

- **Creation of a professional network**

This network, novel in France, aims to federate all research and surveillance actors in the field of antibiotic resistance, to foster collaborations and generate new clinical, epidemiological, veterinary and environmental data. This will accelerate research and improve estimations of the true impact and cost of antibiotic resistance.

- **Creation of a national observatory group dedicated to social sciences**

This observational network, which focuses on the analysis of dialogue, behaviours and social practices linked to prescription, is a key element in understanding the socio-cultural and contextual roots of antibiotic resistance and prescription.

Implementing an international research network with low and middle-income countries

Faced with the growing problem of antimicrobial resistance in resource-limited countries, the national research programme is committed to implementing and coordinating a research network federating inter-country partnerships between national players and scientists to structure responses to future project calls, and reinforce research on antimicrobial resistance. The PPR's ambition is also to develop prevention and control strategies against antimicrobial resistance that are tailored to local populations.

Governance

The national antibiotic resistance programme will be supported by a Steering Committee (French Government - Ministries for an Ecological and Solidary Transition, Solidarity and Health, Higher Education, Research and Innovation, Agriculture and Food - ANR), a Governing body Committee and a Scientific Council.

Expected impacts at national level

- Implement newly discovered strategies and therapeutic innovations to reduce antibiotic resistance by the end of the 10 years.
- Build a pan-national research structure that allows to:
  - Predict the risk of emergence, acquisition and transmission of antibiotic resistance in humans, animals and the environment.
  - Protect humans and animals from antibiotic resistance and prevent contaminations (pollutants, resistant bacteria and resistance genes) likely to increase emergence and the spread of antibiotic resistance in the environment.
  - Implement innovative diagnostic and detection tests, intervention and control measures to contain antibiotic resistance.
  - Educate and empower individuals and communities for appropriate antibiotic use.
  - Possess a new therapeutic arsenal, which generates little or no resistance.
  - Rely on innovative technological tools that respond to health concerns (dampen transmission, antibiotic prescriptions, economic impact, and improve control of an environment free of antibiotic-resistant bacteria).
  - Participate in the fight against antimicrobial resistance in low and middle-income countries through collaborative programmes.

Expected impacts at international level

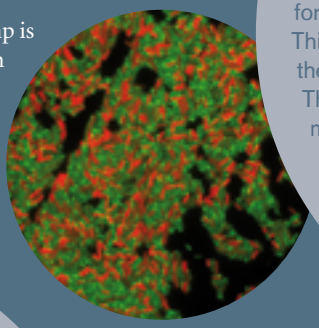
- Similarly to overseas national initiatives (EU countries and the USA), this research programme based on One Health principles aims to:
  - Develop prevention strategies, optimize treatment and reinforce the host's immune response.
  - Break transmission chains, enhance surveillance and improve diagnostic tools.
  - Develop effective infection prevention, control and stewardship strategies.
- A particular focus is placed on social and computer sciences in order to:
  - Identify underlying drivers for antibiotic misuse, raise awareness and encourage behavioural changes at all levels (healthcare workers, patients, veterinarians, farmers and the general population).
  - Address a research gap in the development of digital capacities and machine learning, in agreement with the ongoing national plan on artificial intelligence.
- This national strategy is intended to fully integrate international research programmes, WHO priorities and reinforce ongoing international cooperation (eg. European Joint Programming Initiative on antimicrobial resistance, European Innovative Medicines Initiative, EU joint action against antimicrobial resistance and healthcare-associated infections).

Recent discoveries illustrating examples of research supported by Inserm and its partners:

Acquisition of resistance imaged in real time

By allowing contact between bacteria *(Escherichia coli)* that are resistant or sensitive to the same broadly used antibiotic, tetracycline, the acquisition of resistance by the sensitive bacteria could be visualized for the first time in living cells by fluorescence microscopy. This resistance relies on the ability of the bacteria to expel the antibiotic using efflux pumps located on its membrane. These specific efflux pumps, TetA, excrete antimicrobial molecules out of bacteria, conferring resistance in less than 2 hours. This highlights the need to react quickly.

https://science.sciencemag.org/content/364/6442/778
Science Vol. 364, Issue 6442, pp. 778-782, 24 May 2019. DOI: 10.1126/science.aav6390

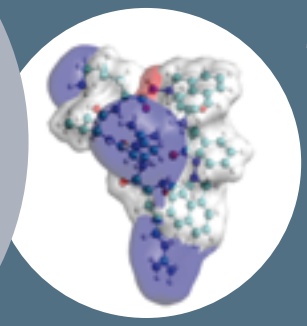


Population of *Escherichia coli*, in which the TetA pump is labelled in red and tetracycline in green. Although genetically identical, some bacteria acquire the ability to produce TetA pumps and expel tetracycline, while others accumulate the antibiotic and fail to develop resistance.
©Christian Lesterlin

Exploiting the properties of a bacterial toxin as new antibiotics

The study of a new bacterial toxin produced by *Staphylococcus aureus*, characterised by its ability to kill other bacteria, led to the development of a new family of powerful antibiotics, active against multi-resistant Gram-positive and Gram-negative bacteria. So far, these molecules appear to generate little to no resistance in animal studies.

PLOS Biology 17(7), 9 July 2019
https://doi.org/10.1371/journal.pbio.3000337



Three-dimensional modelling of a new antibiotic that cause little to no resistance in the tested models. Its efficacy and absence of toxicity make it a promising candidate for the development of alternative treatments against infections caused by resistant bacteria.
©Brice Feldenn

Wastewater and sewage treatment plant
©DedMityay-Adobe Stock

Yellow-legged Gull
©Mohammad-Adobe Stock

Environment, a potential source of antibiotic resistance in Wildlife

Release of antibiotics into the environment can create a reservoir of resistant bacteria and genes, thus constituting a potential source of resistance transmission. Studies on antibiotic resistance in wildlife have identified numerous antibiotic-resistant enterobacteria in Yellow-legged Gulls. These animals live close to human facilities and feed on waste products. Today's research aims to better understand the mechanisms involved in transmission within this colony of Yellow-legged Gulls and identify resistance genes present. It will help us to understand the role of water in such contaminations.

Ongoing project led by Marion Vittcoq, building on a previous publication: https://doi.org/10.1002/ece3.2707

Hospital and urban wastewaters, an important source of antimicrobial resistance in the environment

Human activity has a significant impact on natural ecosystems, and wastewaters have been identified as sources of genetic determinants of antimicrobial resistance (AMR) that may favour AMR selection in the environment. A study conducted on treated and untreated, hospital and urban, wastewaters in France, investigated the AMR genes and microbiota using multi-variate analysis and machine learning. The results emphasised the need for implementation and optimisation of sanitation systems, and are of interest to policy makers for risks associated to wastewaters.

Water Research X, 7: 100045, 1 May 2020.
https://doi.org/10.1016/j.wroa.2020.100045

Design: M. Belkacem, Disc Inserm – Cover illustration from a photo (bacteria culture) by P. Latron©Inserm – April 2020

Scientific contact: evelyne.jouvin-marche@inserm.fr
Press contact: presse@inserm.fr

Inserm
101, rue de Tolbiac
75654 Paris cedex 13 - France
inserm.fr

Inserm