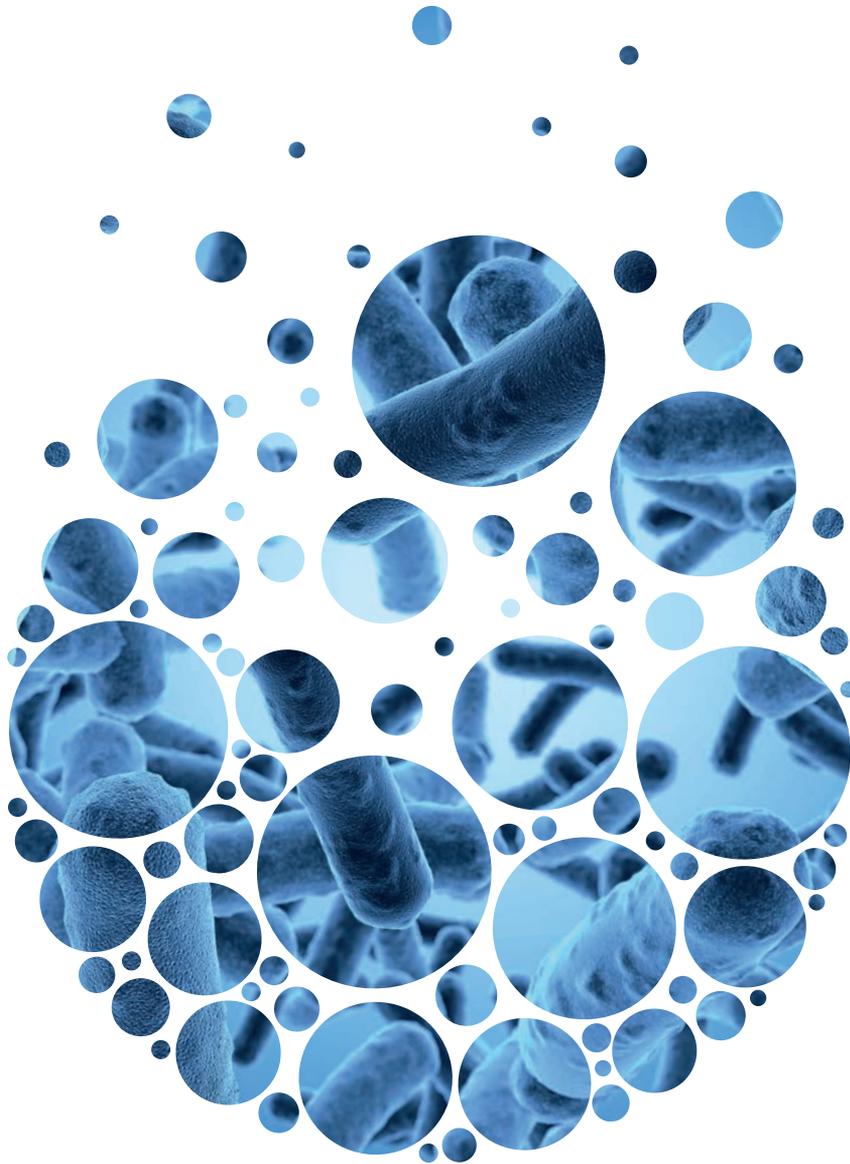




World Alliance Against Antibiotic Resistance



ALLIANCE CONTRE LE DÉVELOPPEMENT
DES BACTÉRIES MULTI-RÉSISTANTES



POLICY TO COMBAT ANTIBIOTIC RESISTANCE: AN IMPLEMENTATION MANUAL

A major public health and sustainable development
challenge for future generations

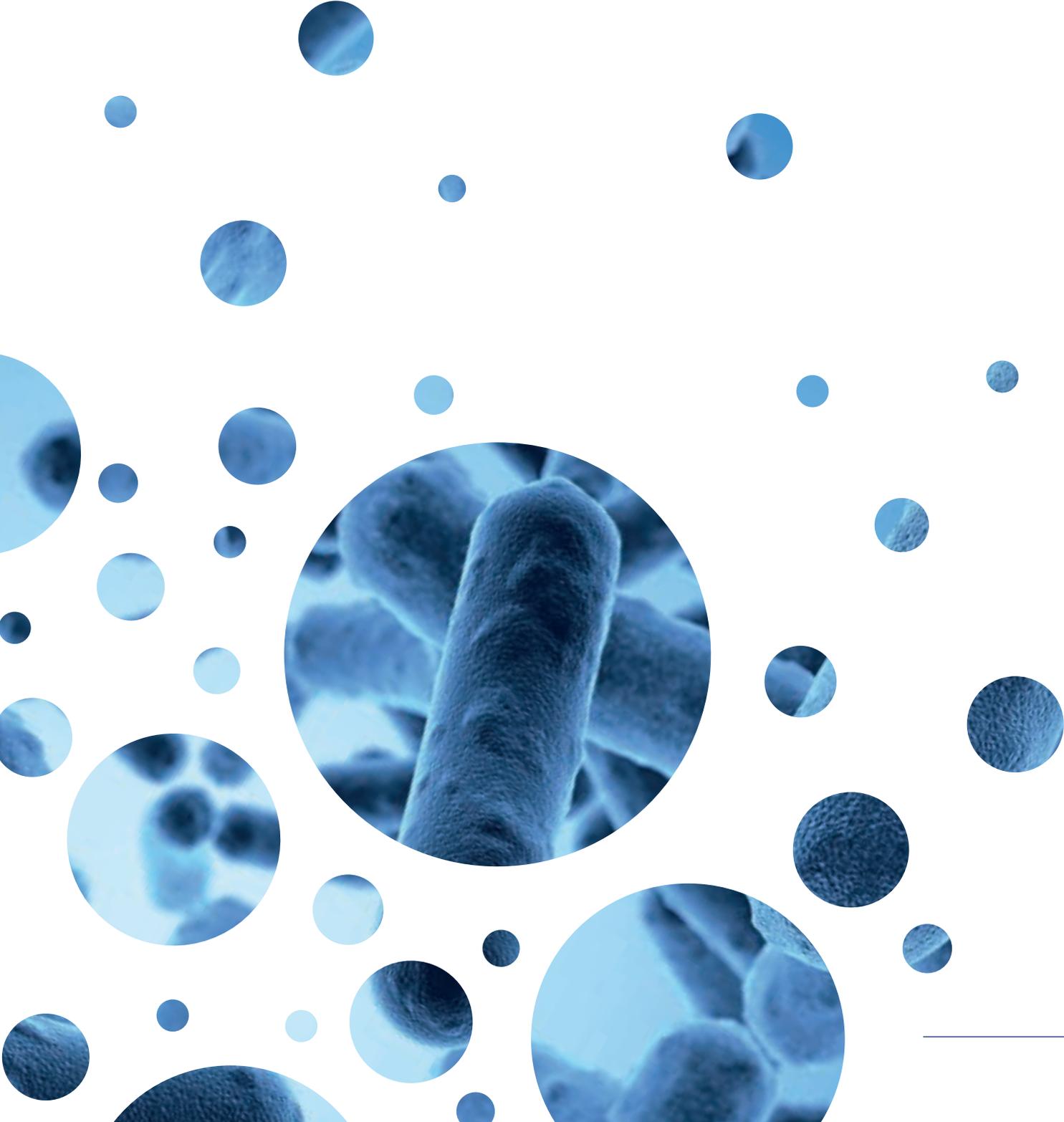
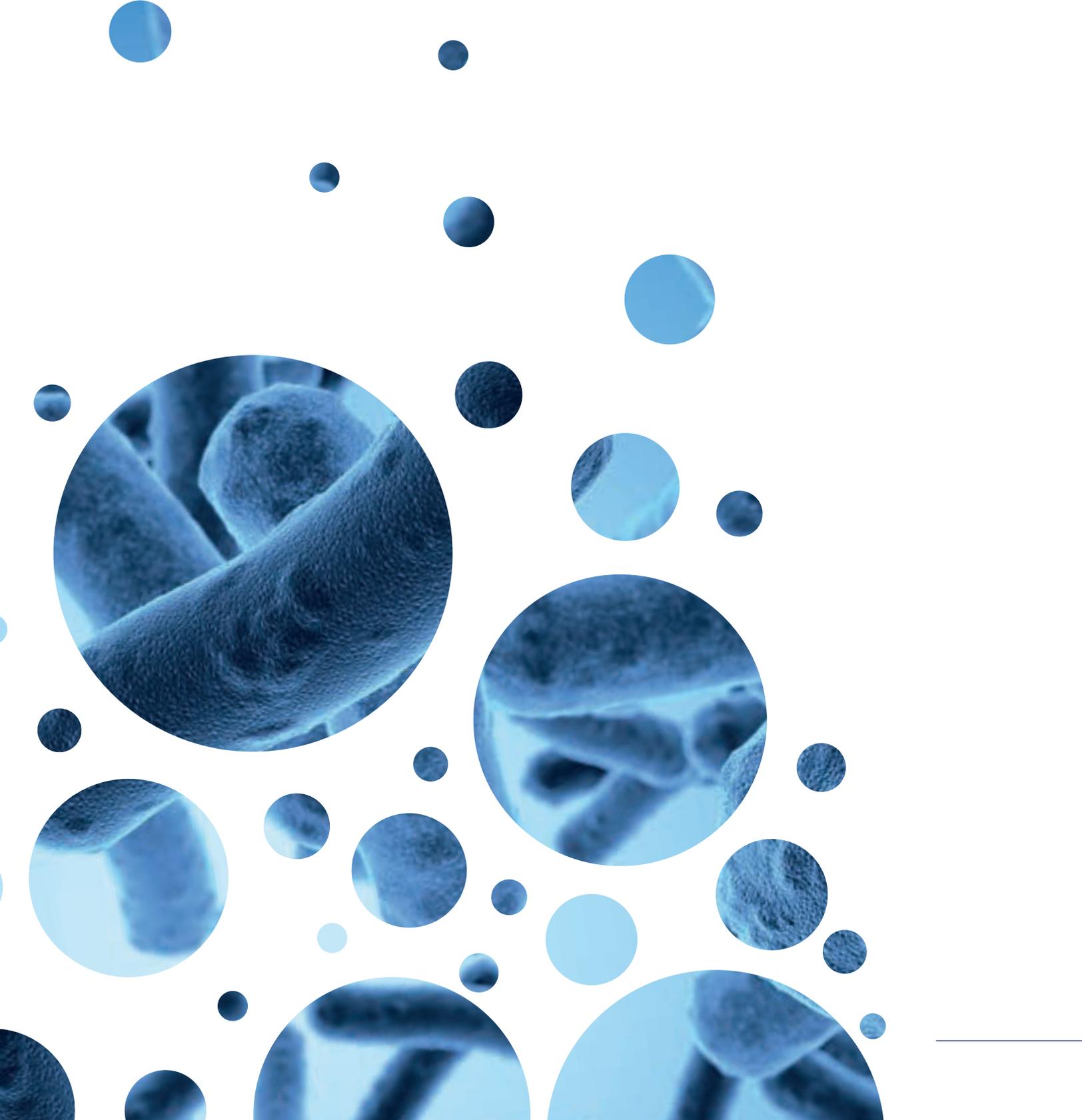


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A model policy implementation manual on combatting antibiotic resistance,
Publication Date: November 2018, originally in French

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INTRODUCTION

First of all, we would like to thank everyone who contributed to the development of this manual. Many experts in human health, animal health and the environment participated in the research and revision process to make this document a practical guide to fighting daily against antibiotic resistance. We would particularly like to thank the "World Alliance Against Antibiotic Resistance" (ACdeBMR/WAAAR) group for the energy it deploys daily to highlight this phenomenon.

Antimicrobial resistance is a worldwide phenomenon which is not sparing France. French consumption of antibiotics, while more moderate than in other countries, is significant compared to the European average, and consumption in community medicine has grown by 8.6% over the last ten years. Preventing the spread of resistant bacteria in the population through hygiene measures can also be improved upon in our country. Even if our knowledge of the subject is still limited, it appears that public policy follow-up must continue. This finding has translated into political momentum whose origins can be traced to several political leaders gathered on 12 November 2018 to present the work of the working group.

Human health, animal health and the environment are all concerned with this problem. Indeed, antimicrobial resistance affects all ecosystems and living things, as the One Health concept perfectly demonstrates.

This instruction manual was written in order to help transmit this knowledge and promote the fight against antibiotic resistance. It is intended to be simple, precise and visually appealing. The manual aims to raise awareness for all stakeholders, from citizens to public authorities, by providing information and advice to apply in everyday life in order to bring about the collective consciousness needed to fight against antibiotic resistance. The simplicity of the document aims to optimise the message conveyed by the policy and scientific recommendations used for its writing. It is our collective duty to fight against antibiotic resistance and we all can, each at our own level of responsibility, build together a world in which resistance is under control and there is a greater security.

Éric Alauzet, MP for the department of Doubs, France

Yves Daudigny, Senator of Aisne, France

I. WHAT IS ANTIBIOTIC RESISTANCE?

1. Some background information



The bacterial world, in equilibrium with Man

A bacterium is a unicellular microorganism, neither animal nor plant, whose genome consists of a single DNA chromosome. Demonstrating extraordinary plasticity and diversity, bacteria have colonised every environment on earth, even the most extreme. Bacteria are necessary for life on Earth and for human survival: they notably participate in the food digestion process.

Nonetheless, some bacteria may be pathogenic for humans, and the bacterial infections they cause can be deadly. Some have even had dramatic consequences on the human species and caused millions of deaths, such as: *Mycobacterium tuberculosis*, the agent responsible for tuberculosis, *Yersinia pestis*, responsible for the plague, or *Vibrio cholerae*, responsible for cholera.



Antibiotics, a means of defence from bacteria

Since Alexander Fleming's accidental discovery of the properties of *Penicillium* fungus to produce penicillin in 1928, followed by René Dubos' discovery of gramicidine produced by the bacteria *Bacillus* in 1930, or even the discovery of sulphonamides, the first synthetic antibiotics, by Gerhard Domagala in 1935, Man has used antibiotics to cure bacterial diseases that were often fatal until then.

Antibiotics are molecules possessed with the ability to kill (bactericidal effect) or limit the multiplication (bacteriostatic effect) of bacteria. They are used in human and veterinary medicine to fight against bacterial infections and can have natural or synthetic origins. There are many antibiotics which have been divided into different families, (penicillins, macrolides, sulfonamides ...). Antibiotics are very effective against bacterial infections but have no effect on viral infections.



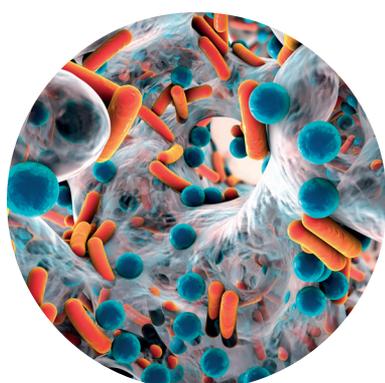
Antibiotic resistance, or entry into the post-antibiotic era

Antibiotic resistance is the result of certain bacteria's ability to defend themselves against antibiotics by adapting their genome (mutations or transfer of resistant genes between bacteria).

Concretely, the phenomenon of antibiotic resistance leads to situations where patients with infections caused by a resistant bacterium will struggle to heal despite the antibiotic treatment they are receiving. By staying sick for longer periods, the risk of complications increases, and their chance of survival are reduced.

According to the World Health Organization (WHO), if we do not take emergency measures, we will soon enter a „post-antibiotic era“ characterised by a rise in the number of fatalities from infections and simple injuries due to a lack of effective antibiotics.

2. Mechanisms of Antibiotic Resistance



Antibiotic resistance, a biological phenomenon of adaptation...

Never alone in their environment, bacteria live in communities with complex interrelations, exchanging, among other things, their antibiotic-resistant genes. All bacteria, such as those coming from our intestinal flora or those residing in the soil, participate in these gene exchanges. These exchanges amplify the phenomenon of antibiotic resistance. Antibiotic resistance is one of the components of resistance to different types of antimicrobial agents, commonly referred to as AMR (antibiotics, antivirals, antifungals and antiparasitics).

Man is not the root cause of the antibiotic resistance phenomenon: bacteria have always adapted to survive. It is the very principle of natural selection. For example, in Canada, drilling operations in permafrost have helped reveal the existence of 5000-year old bacteria with antibiotic-resistant genes.

...terribly worsened by the action of mankind



Antibiotic resistance is the harmful consequence of two synergistic causes related to human activity: overuse of antibiotics in human and animal health, which leads to the selection of the most resistant bacteria and the dissemination of these selected bacteria, either by direct transmission within human and animal populations ("cross-transmission"), and indirect via the environment. The organisation of our health system, overuse of biocides (antibiotic-resistant genes are often associated with some biocide-resistant genes such as antiseptics and disinfectants), and long-term hospital stays are also major factors which have aggravated the development of antibiotic resistance.

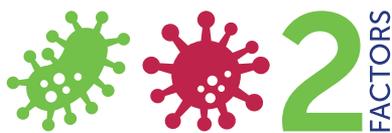
It should be noted that the increase in antibiotic resistance is, today, more moderate in Europe than it is in countries such as India or China, which combine high-consumption of antibiotics, high densities of human and animal populations and weaker environmental hygiene with scope for improvement.

However, the phenomenon of antibiotic resistance is such that, even in France, an increasing number of bacteria is accumulating resistant genes that threaten to make even the most recent antibiotics obsolete in the short term.

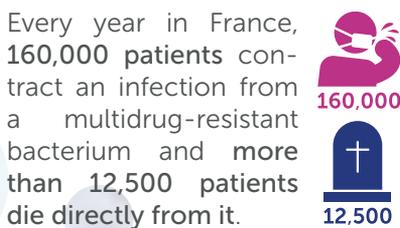
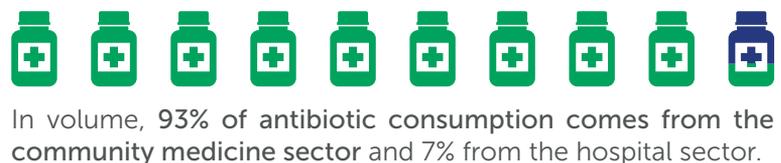
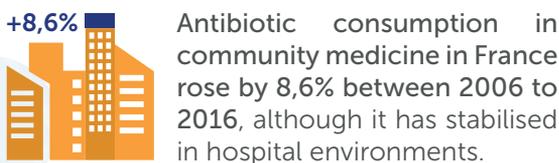
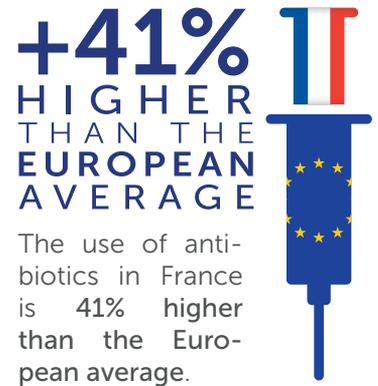
II. ANTIBIOTIC RESISTANCE: A PHENOMENON WITH MULTIPLE IMPACTS

1. A few facts and figures on the Sanitary Challenges of Antibiotic Resistance

The development of antibiotic resistance is linked to two factors related to human activity: overconsumption of antibiotics and the cross-transmission of antibiotic-resistant bacteria.



In 2015, France was ranking 4th among European countries in terms of antibiotic consumption behind Greece, Romania and Belgium.



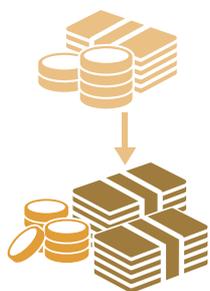
ANTIBIOTIC RESISTANCE LEADS TO INCREASED MORTALITY

Antibiotic resistance leads to increased mortality as it limits therapeutic options for bacterial infections.



Key takeaways: Antibiotic resistance is a major public health issue in France and the world. It is estimated that, in France, more than 12,500 patients die every year from the consequences of antibiotic resistance. It is urgent to act without delay.

2. The Economic Impact of Antibiotic Resistance

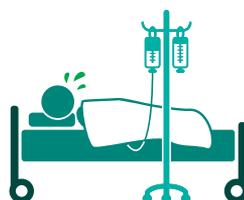


Antibiotic resistance is estimated to cost the United States 55 billion dollars and 1,5 billion euros to Europe. The cumulative cost of antibiotic resistance could exceed 100,000 billion dollars by 2050 if nothing is done to fight against resistant bacteria.



In France, the overconsumption of antibiotics in community medicine leads to an **additional expenditure of 71 million euros compared to the European average**, and of 441 million euros compared to the most virtuous countries.

In France, 97,6 million boxes of antibiotics were reimbursed by the public health insurance in 2013. However, **between 30% and 50% of antibiotic therapies are useless or inadequate.**



Some of the additional costs linked to the overconsumption of antibiotics also include **lengthened hospital stays** necessary to treat drug-resistant bacterial infections.

NOT ONLY SAVES LIVES BUT **ALSO MONEY**

The costs associated with resistant infections are important and hospital strategies to control resistant bacteria not only save lives but also saves money.



Key takeaways:

The development of antibiotic resistance has a considerable impact on our public finances and on the efficiency of our health system.

3. Environmental Consequences of Antibiotic Resistance



Bacteria which are resistant to antibiotics, as well as those resistant to other biocides, disseminate through exchanges between different sectors of the environment (human and animal populations, wastewater, soils, plants...). **Every living being is affected by antibiotic resistance.**

The concentration of antibiotics in river water increases with the presence of humans. This concentration is particularly important downstream of health establishments, farms and close to discharge points (purification stations...), thus favouring selection pressure of resistant bacteria.



Resistant genes are found in bacteria inhabiting every environment modified by human presence, as human activities contribute to the spread of antibiotic resistance in the environment.

Wild animals living in areas modified by human activity are more likely to carry multidrug-resistant bacteria. **Exchanges of multidrug-resistant bacteria occur between wildlife, domestic animals and humans.**



Resistant bacteria, their resistance genes and antibiotic residues slowly degrade in nature and can accumulate there.



Key takeaways:

Contamination of the environment by multi-resistant bacteria, genes of resistance and antibiotic residues, contribute to the development of antibiotic resistance and enhance contamination of the human being. Antibiotic resistance can threaten all forms of life and ecosystems: it is a major sustainable development issue.



IV. A WORLDWIDE AWARENESS OF THE CHALLENGE OF ANTIBIOTIC RESISTANCE

1. Antibiotic control is a new global priority



Top-level political, institutional and scientific authorities have begun engaging on the issue of antibiotic resistance.

In 2015, the WHO launched a Global Action Plan on AMR, (Antimicrobial Resistance – AMR – includes resistance to antibiotic, antiviral, antifungal and anti-parasitic medicines), with the aim to preserve our ability to prevent and treat infectious diseases by using safe and efficient medicines. The General Assembly of the United Nations, which does not often address health-related issues (it had done so for the AIDS and Ebola virus), discussed the matter in September 2016 and committed to adopting a coordinated approach to face the fundamental causes of resistance in several sectors, including human health, animal health or agriculture.

The European Union (EU) also included the sanitary risk posed by antibiotic resistance in its policies. A five-year action plan against AMR (Antimicrobial Resistance) was initiated in 2011, followed by a new plan presented in 2017, encapsulating both human and animal health as per the “One Health” approach.



Leading politicians are raising against AMR

Barack Obama, former President of the United States (2008 – 2016)

„Antibiotic resistance is one of the most pressing public health issues facing the world today.’

David Cameron, former Prime Minister of the United Kingdom (2010 – 2016)

„If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work, and we are cast back into the dark ages of medicine where treatable infections and injuries will kill once again.’

2. France, an active player in antibiotic resistance control



Campaigns aiming to reduce consumption of antibiotics...

France has been active in reducing its consumption of antibiotics for a long time. Throughout the 2000s, awareness campaigns, revolving around the catchphrase “Antibiotics aren’t automatic” (« Les antibiotiques, c’est pas automatique ») and the two successive Éco-Antibio plans have successfully reduced consumption in urban communities and veterinary medicine. Progress was also made in controlling the epidemic spread of multidrug-resistant bacteria through hygiene-enhancing measures, particularly in healthcare institutions.

Human health plans

Overall, three national plans were developed to preserve the efficacy of antibiotics, and have taken the form of multi-year action plans: 2001-2005, 2007-2010 and 2011-2016. Designed to introduce reason and control in antibiotics prescriptions, their objective has been reached as a study published in 2009 by the journal, PLoS Medicine, claimed that there had been a reduction of 26.5% of antibiotics prescription over five years.

Nonetheless, these efforts slowed as the campaign directed toward the general public ended, and antibiotic consumption surged again (+8.6% in community medicine from 2006 to 2016).

Éco-Antibio plans in the animal world

Co-constructed with representatives from agricultural and veterinarian professional organisations, and scientists and representatives from veterinarian pharmaceutical companies, the ÉcoAntibio plan for 2012-2017 was implemented by the Ministry of Agriculture and led to a 37% decrease in antibiotic consumption in veterinary medicine in France . The plan was so successful that it was renewed in January 2018 for 2017-2021.

... but insufficient awareness in the political sphere.

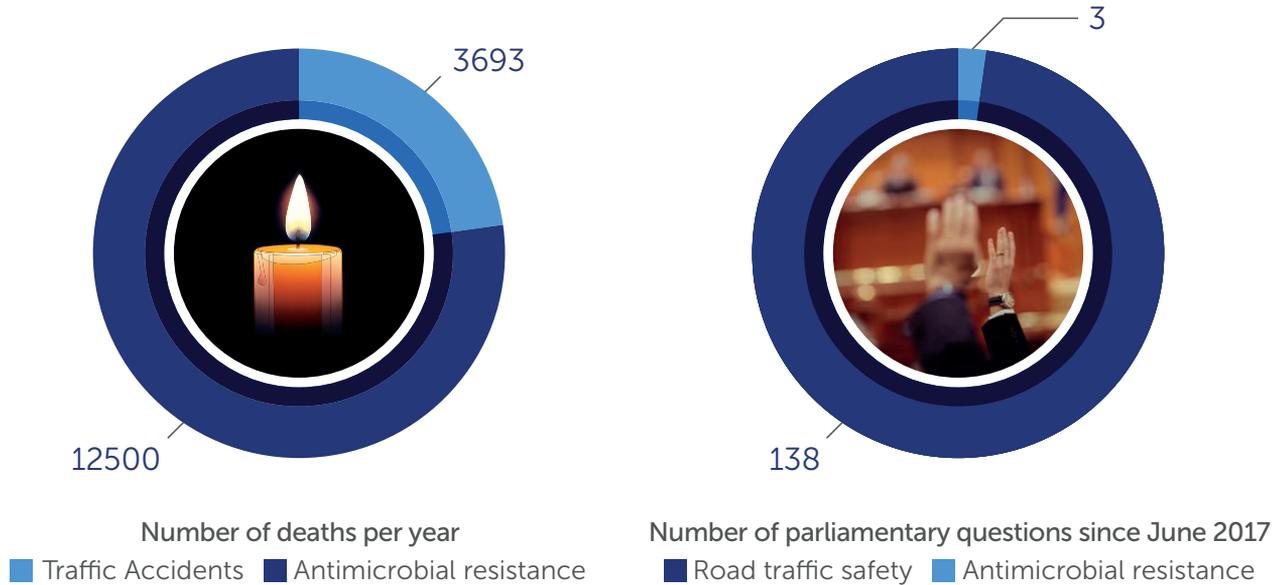
As opposed to Barack Obama, no French Head of State or government took a firm public stand on antibiotic resistance.

In November 2016 , the Minister of Social Affairs, Health and Women’s Right, Marisol Touraine, announced the government’s full commitment in controlling antimicrobial resistance following the publication of a report redacted by Dr Jean Carlet which was based off the work of a panel of specialists.

Despite this announcement and the instalment of an Inter-ministerial Committee for Health (CIS), as well as the appointment of a Ministerial Delegate on antimicrobial resistance in the Ministry of Health, the topic is scarcely discussed in the Parliament, even though antimicrobial resistance control is one of the objectives of the new National Healthcare Strategy which was unveiled in December 2017 by Agnès Buzyn, the Minister of Solidarities and Health since May 2017.



In comparison to other topics such as road safety, political consideration for antimicrobial resistance is not proportional to the fatalities associated with it (see Annex 1).



Key takeaways:

Today, the highest institutional, political and scientific authorities of the world (UN, WHO, EU...) are committed to making antibiotic resistance control a public health priority. The EU has, for example, launched a second plan dedicated to this topic.

Numerous scientific and technical recommendations are available.

Unfortunately, while the topic has been addressed by the public authorities starting in 2016, it is currently rather absent from political discussions.

Antibiotic resistance control is a priority in the National Health Strategy 2018-2022. Political impetus is now required to use every tool available and contain the continued development of antibiotic resistance in France.

V. WHAT CAN BE DONE TO FIGHT ANTIBIOTIC RESISTANCE ON A DAILY BASIS?

Antibiotic resistance is a phenomenon that concerns us all. From political, scientific, international, national and local officials responsible for promoting public policies, to medical and veterinary staff, antibiotics prescribers, and even patients and citizens. By changing our behaviour, we can all be actors committed to the fight against antibiotic resistance.

1. Making appropriate antibiotic use a priority

Prevention, information and training must be at the core of any effective strategy against the development of antibiotic resistance. These measures must be intended for human health professionals, veterinarians who prescribe antibiotics and also the public at large. The objective is to avoid unnecessary prescriptions and to adapt treatment periods for patients in real need of antibiotics by promoting shorter treatments which will reduce the volume of antibiotics consumed.

What I can do:



I am a representative of the public authorities, a parliamentarian or a local elected representative:

- Relaunch national communication campaigns, similar to those of the 2000s, to raise awareness of the necessary sobriety in using antibiotics to the general public.
- Set up communication campaigns targeted at general practitioners by raising awareness of Antibiotic resistance challenges and giving them tools to avoid unnecessary prescription of antibiotics.
- Train health students, and especially future general practitioners or veterinarians, in the challenges of antibiotic resistance and the particularities of the prescription of antibiotics.
- Include a training module on antibiotic resistance and the correct use of antibiotics in the continuing education of human and veterinary health professionals.
- Include a training module on antibiotic resistance and the correct use of antibiotics in the curriculum of health students.
- Generalise the sale of the antibiotics per unit in order to deliver only the exact necessary quantity to avoid inadequate extension of the treatment, or even future self-medication of the patient or their relatives.
- Promote vaccination, in line with the current prevention policy, to reduce risks.
- Harmonise at regional or national level the information manuals on antibiotics and facilitate their access through digitalisation to ensure all concerned professionals use the same recommendations.



I am a human or veterinary health professional:

- Provide each patient or animal owner who has received an antibiotics prescription with an information sheet on antibiotics, their proper use and the risks of antibiotic resistance, during the visit at the doctor's office, at the pharmacy or in the veterinary care facility.
- Use Rapid Diagnostic Orientation Tests during consultations to determine the exact origin (bacterial or viral) of infections.
- Prescribe antibiotics only when necessary, in accordance with the recommendations in force, and limit the duration of prescriptions.
- Vaccinate my patients.



I am a citizen:

- Trust my doctor to prescribe the therapies I need and not prescribe antibiotics when deemed not necessary.
- Not to hesitate to ask my doctor or veterinarian about the consequences of antibiotics.
- Ask to be vaccinated and have my pets vaccinated.



Rapid Diagnostic Orientation Tests, essential tools in the fight against Antibiotic resistance

Rapid Diagnostic Orientation Tests enable the establishment of a first diagnosis by indicating, for example, whether a patient suffers from a bacterial or a viral infection.

For example, 90% of pharyngitis (tonsillitis) are of viral origin, and thus do not require antibiotic treatment. A quick and easy test is available and can be performed by doctors, and even by pharmacists.

Many other tests are available on the market. Unfortunately, their use by doctors remains relatively low, although they are an effective way of combating unnecessary antibiotics prescriptions, and therefore antibiotic resistance.

2. Prevent cross-transmission

Cross-transmission is the transmission of resistant bacteria (or other microorganisms) from patient to patient, from animal to animal, from humans and animals to the environment and from the environment to humans and animals. Cross-transmission can occur through direct contact (especially hands), coughing, or through indirect sources such as water and food containing bacteria excreted by humans and animals. Hygiene rules must be taken very seriously by every healthcare professional practising in a health facility or on their own, be they doctors, nurses, caregivers, physiotherapists, or animal health professionals.

What I can do:



I am a representative of the public authorities, a parliamentarian or a local elected representative:

- Increase the development of awareness campaigns on the respect of basic rules of hygiene, including hand hygiene, in the general population, schools, other communities, and of course for health staff and home carers.
- Ensure that each school in my city / department / region provides students with clean toilets, equipped with adequate handwashing equipment (sinks, soap, disposable towels) and a poster explaining why, when and how to wash your hands.
- Strengthen the training of future health staff on hygiene measures, targeting actions on the risks of transmission of multi-resistant bacteria.
- Encourage scientific research on the identification of risk factors for cross-transmission, including cross-intrafamily transmission.
- Include a training session on hand hygiene in the public presentations given by healthcare students.



I am a human or veterinary health professional:

- Always apply infection prevention and control protocols.
- Inform patients about infection prevention, hygiene, and proper use of antibiotics.
- Follow the recommendations of the Hospital Hygiene Society (SF2H): wear a short-sleeved outfit, have short nails and wear no hands or wrists jewel at work.
- Disinfect my hands with hydroalcoholic solutions: 1 / Before touching a patient; 2 / Before an aseptic gesture; 3 / After a risk of exposure to a biological fluid; 4 / After touching a patient; 5 / After touching the environment of a patient.



Je suis un citoyen :

- Protect my environment by avoiding to contaminate others when I am sick.
- Disinfect my hands frequently, with a hydroalcoholic solution if possible, after using the bathroom, after sneezing or coughing, or after having been in contact with an animal, in order to prevent the transmission of resistant bacteria.
- Avoid contact with vulnerable people when I am likely to have an infection.

3. Encourage research

A “mad arms race between Man and bacteria”. As soon as a new antibiotic is used, the bacteria adapt, and new resistances appear. Besides, there is a need for progress in order to fully understand antibiotic resistance, its transmission and its impact on the environment. Progress also needs to be made in the search for new antibiotics. Finally, the measurement of the multiple impacts of antibiotic resistance requires more effective evaluation methods.

What I can do:



I am a representative of the public authorities, a parliamentarian or a local elected representative:

- Propose a set of indicators to measure the evolution over time of antibiotic resistance as well as its cost and health consequences, in the different sectors (human, animal and environmental).
- Contribute to the financing of scientific and sociological research on antibiotic resistance in general, and in particular to understand its transmission between the various compartments of our biotope.
- Develop ways to use artificial intelligence (AI) notably to assist in prescriptions, among other things.
- Create incentives and technical support encouraging pharmaceutical companies, but also start-ups, to develop new antibiotics, alternatives to antibiotics, and new tests for rapid diagnosis of infections.
- Facilitate marketing and access to innovative products in the field of bacterial infections.



I am a human or veterinary health professional:

- Ensure that adverse events related to multidrug-resistant bacteria are reported to the competent authorities.

4. Prevent the risks of environmental contamination

The impact of humans on their environment is well established. Resistant bacteria, their resistance genes as well as the antibiotics themselves, are continually released into natural environments from human settlements and farms and constitute true biological pollutants. Spreading through water and soil, then coming into contact with other bacteria, flora and fauna, exchanges contribute to the development of antibiotic resistance at all levels of the biotope. However, we are still unable to fully understand the consequences of such a phenomenon, but we already know that resistant bacteria released into the environment can, in turn, contaminate us.

What I can do:



I am a representative of the public authorities, a parliamentarian or a local elected representative:

- Strengthen sanitation and requirements regarding wastewater discharge and treatment to reduce pollution and the associated mortality stemming from the release of resistant bacteria, and that of antibiotics, into the environment.
- Classify multi-resistant bacteria and their resistance genes as pollutants dangerous for the environment and human health, as is done for certain heavy metals (mercury, lead, etc.) or other toxic chemicals.
- Enforce rational use of disinfectants and biocides in the establishments and structures I am responsible for, to prevent their spread in the environment.



I am a human or veterinary health professional:

- In farming, prescribe antibiotics only when necessary and encourage vaccination.
- Reasonably use disinfectants and biocides at my workplace to avoid the spread of bacteria in the environment.
- Be concerned about how the effluents are discharged from the healthcare facilities where I work and the husbandry facility where I operate.



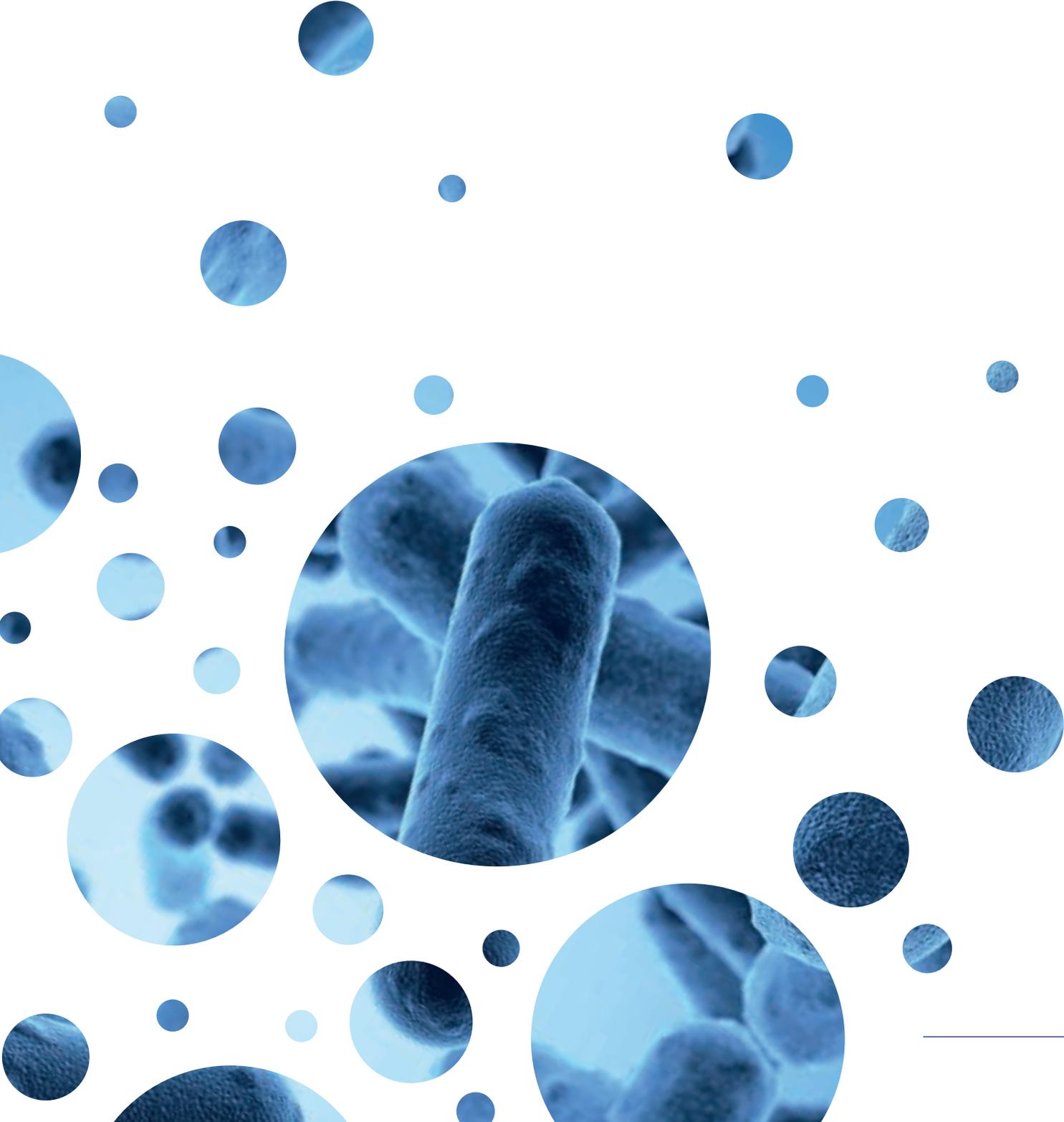
I am a citizen:

- Return all unused antibiotics to pharmacies to avoid potential future self-medication and to avoid disposal of antibiotics in the ordinary garbage.
- Reasonably use disinfectants and biocides at home to prevent their spread in the environment.
- Avoid human discharges directly into the environment, outside of sanitation systems.

ANNEX 1

Compared to other topics such as road safety, the political focus in France on antibiotic resistance is inversely proportional to the mortality associated.

Parliamentary questions on road safety in the National Assembly during the XVth legislature:	107
In the Senate (since June 2017):	31
Parliamentary questions on antimicrobial resistance in the National Assembly during the XVth legislature:	3
In the Senate (since June 2017):	0
Number of deaths on the roads:	3,693 people in 2017
Number of deaths from antimicrobial resistance-related causes:	More than 12,500 per year



CONTRIBUTIONS

The association World Alliance Against Antibiotic Resistance (AC2BMR/WAAAR), presided by Doctor Jean Carlet, gathers more than 750 members from over 56 countries and is supported by 125 scientific groups and societies. Created in 2011, its goal is to enhance the fight against antibiotic resistance in France and in the world. The association has been steering this Instruction Manual project since launch in 2018.

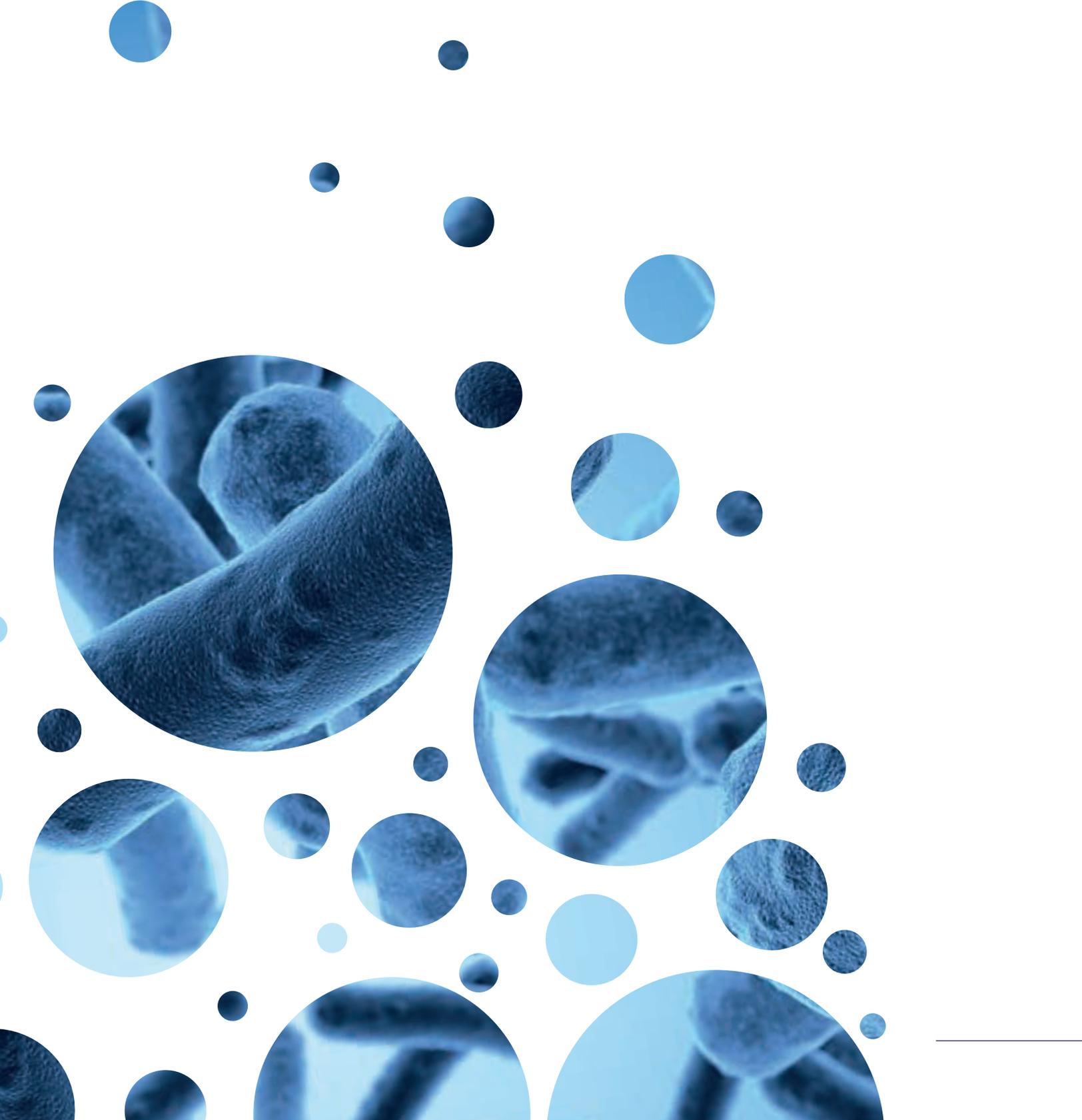
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