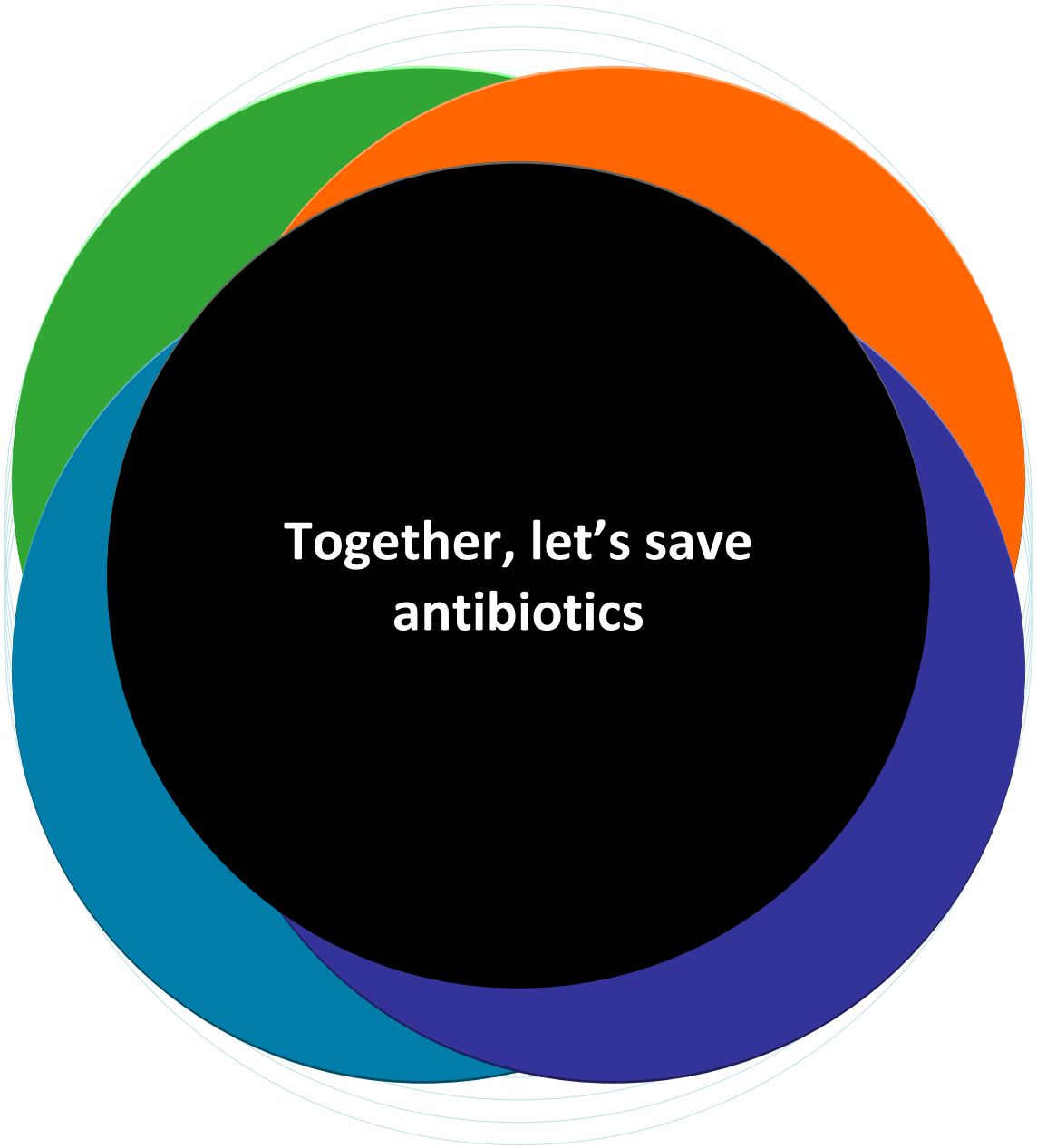
Proposals of the special working group for keeping antibiotics effective



Written by : Dr Jean CARLET and Pierre LE COZ

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MINISTÈRE
DES AFFAIRES SOCIALES,
DE LA SANTÉ
ET DES DROITS DES FEMMES

REPORT FROM THE SPECIAL WORKING GROUP FOR KEEPING ANTIBIOTICS EFFECTIVE

June 2015

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Thank you to the members of the plenary group for their unwavering investment throughout the assignment (**page 76**).

Last but not least, my warmest thanks go to **Pierre le Coz**, public health student, for his excellent work. His role in producing this report has been decisive.

May this team effort go some way towards keeping antibiotics effective.

Executive summary

158,000 multidrug-resistant bacterial infections in France

12,500 deaths linked to a multidrug-resistant bacterial infection in France

Between EUR 71 million and EUR 441 million spent on antibiotic overuse in France

Research and funding for combating antimicrobial resistance are poorly coordinated

No new antibiotic with a new mechanism of action has been developed for 20 years

The rise in resistance stems to a large extent from pollution and human activities

Today, microbial resistance to antibiotics (antimicrobial resistance) is a serious public health problem that is gaining swift ground. Despite action taken by the World Health Organisation (WHO), **the number of victims (mortality, morbidity) is steadily rising, and the outlook is increasingly bleak**. With the pressing need for **new therapies to be found, the efficacy of existing antibiotics to be maintained and the spread of resistance in the environment to be limited**, many countries have recently launched ambitious plans, particularly the United States (US) and United Kingdom (UK).

In France, every year **more than 150,000 patients** develop a multidrug-resistant bacterial infection, from which more than **12,500 of whom never recover**. In addition to the human cost there is a considerable economic cost, mainly resulting from the **overuse of antibiotics in France**. A poor European example, France spends between **EUR 71 million** (compared with the European average) and **EUR 441 million** (compared with the average of the most virtuous countries – i.e. those consuming the least antibiotics) more than its neighbours on antibiotic treatments in the community (primary care) sector.

However, the fight against antimicrobial resistance can no longer be waged solely through the **essential change for the better in healthcare professionals' prescribing practices**. As a result, alongside overuse in human and animal medicine alike, as well as in non-health-related uses such as intensive farming, are the **ecological effects of the dispersal of antibiotic residues in the environment. The pollution of different reservoirs of life by human activities** (anti-infectives, heavy metals, chemical agricultural inputs, etc.) fosters the selection of resistance in natural environments under attack. Moreover, it is important **not to restrict discussions on antimicrobial resistance to the use of antibiotics alone**. Misuse of disinfectants and biocides, including by households, may contribute to cross-selection of resistance.

Lastly, manufacturers find themselves in **a paradoxical situation**: antibiotics are hi-tech products, and yet they are inexpensive and their use needs to be limited. Today, investing in antimicrobial innovation is no longer profitable. It is therefore necessary to **find a new medico-economic model** that allows for sufficient return on investment, in order to encourage fresh investment in the development of new products that help combat antimicrobial resistance.

With a view to coming up with original, concrete, practicable ideas, over 120 qualified experts from a range of backgrounds willingly responded to the call launched by the French Health Minister at the start of 2015. The assignment entrusted to Dr Jean Carlet thus brought together healthcare professionals, researchers, academics, members of patients' associations, representatives of the pharmaceutical industry and biotechnology, alongside health agencies and the various administrative departments. **Together, these stakeholders have drawn up recommendations aimed at bringing about a paradigm shift and at cutting French antibiotic use by a quarter.**

Four major objectives have been set with a view to limiting the occurrence and spread of antimicrobial resistance. It is imperative that:

- **objective 1:** research be taken further, particularly on new products that can combat antimicrobial resistance
- **objective 2:** more careful monitoring be carried out of how the phenomenon is progressing overall, via standardised, shared indicators
- **objective 3:** antibiotic use be improved
- **objective 4:** population awareness of responsible antibiotic use be heightened

Given the importance and complexity of the challenges, an ambitious programme must get public authorities involved alongside public health, environment and industry stakeholders. The working group therefore recommends that Madam Minister and, more broadly, that the Government as a whole:

- set up **an interministerial committee in charge of coordinating the fight against antimicrobial resistance,** steered by **an interministerial delegate** with support from **steering committees dedicated specifically to research, innovation and communication**;
- draw up a **National Interdisciplinary Plan on Antimicrobial Resistance Research**, by allocating the necessary resources to this plan for 5 years, in order to gain a full understanding of the phenomenon;
- support the development of innovative products against antimicrobial resistance by creating a **specific status**;
- in 2016, declare the fight against antimicrobial resistance a "Grande cause nationale" (**Major national cause**).

If these key measures are not set up, **the situation can only get worse**. It is therefore vital that **the necessary financial and human means for carrying out the various target actions set out by the working group are put in place**. This particularly means improving the quality of antibiotic prescriptions and the general level of knowledge on antimicrobial resistance, as well as supporting private and public actions in favour of combating antimicrobial resistance.

More than just producing a report, the stakeholders called on by the French Health Minister wanted to launch a "call to arms". **If nothing changes soon, antimicrobial resistance will paralyse our healthcare system,** which is still founded on the "miracle of antibiotics". Let's not wait for a sudden deterioration in the situation to act. **It is time for society as a whole to take action if we don't want to return to a world without antibiotics.**

Let's find out how to drastically reduce the human and economic cost of antimicrobial resistance by pooling our efforts: **give us 5 years to achieve a paradigm shift!**

Engagement letter

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MINISTÈRE DES AFFAIRES SOCIALES, DE LA SANTÉ
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La Ministre

Paris, le 22 DEC. 2014

CAB POS/DA/MB/ Me D14-3138

Monsieur le Président,

La résistance bactérienne aux antibiotiques augmente régulièrement et menace directement et gravement la santé publique au niveau mondial. Très peu de nouveaux antibiotiques ont été produits ces dernières années et très peu sont attendus dans un avenir proche. Il faut donc mettre en place des actions très concrètes pour sortir de l'impasse thérapeutique actuelle. Si les causes de cette augmentation de la résistance aux antibiotiques sont multiples, la consommation très élevée, erronée ou inadaptée d'antibiotiques en est la cause principale. Il faut de façon urgente innover, en particulier, mais pas uniquement, dans trois grands domaines : la communication et l'information, en particulier du grand public, les comportements de prescription des professionnels, l'attractivité en matière notamment de recherche industrielle pour le développement de nouveaux antibiotiques ou de nouvelles stratégies thérapeutiques et de nouvelles méthodes diagnostiques.

La mobilisation internationale pour éviter une ère « post antibiotiques » reste forte. Ainsi, au-delà du « programme One Health », de nombreux pays, dont notamment les Etats-Unis d'Amérique ou le Royaume-Uni ont lancé des groupes de réflexion pour dégager des pistes crédibles en vue de préserver les antibiotiques.

C'est pourquoi j'ai décidé la mise en place d'un groupe de travail spécial sur la préservation des antibiotiques, dont je vous confie la présidence. Ce groupe de travail comprend des personnalités qualifiées d'horizons divers, des représentants des sociétés savantes, des organismes de recherche, des partenaires industriels, des agences sanitaires, de la Caisse nationale de l'assurance maladie des travailleurs salariés (CNAMTS), des associations de patients. Elle aura le soutien logistique des services de mon ministère, en lien avec les autres ministères concernés.

Le groupe de travail devra proposer pour chacun de ces trois axes stratégiques au moins une action phare (éventuellement déclinée en sous actions), très concrète, de faisabilité étayée et de nature à crédibiliser l'ambition du gouvernement de réduire de 25% la consommation d'antibiotiques d'ici la fin 2016. Ces propositions doivent s'articuler avec les actions en cours de finalisation comme la mise en place du pilotage régional de l'antibiothérapie reposant sur le suivi local des consommations et des résistances, les travaux sur le développement par les éditeurs de logiciels métiers et la finalisation des recommandations du comité de l'antibiogramme de la Société française de microbiologie (CASFM) permettant la généralisation des antibiogrammes ciblés pour les infections urinaires.

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La communication vis-à-vis du grand public et des professionnels de santé doit être renforcée dans son efficacité, par exemple par la mise en place d'une campagne d'information de grande ampleur, du type de celle qui avait été mise en place par la CNAMTS au début des années 2000 (« Les antibiotiques, c'est pas automatique »). Des objectifs chiffrés doivent être annoncés à cette occasion, en demandant une action conjointe entre les prescripteurs et les usagers du système de santé, qui doivent coopérer sur un tel objectif. Il est attendu du groupe de travail spécial des propositions innovantes en matière de communication.

La prescription des antibiotiques reste un acte banalisé dans notre pays. Beaucoup de médecins prescrivent des antibiotiques pour des infections virales. On estime à 30/40% la proportion de traitements antibiotiques inutiles. La France reste dans le peloton de tête des pays les plus prescripteurs d'antibiotiques en Europe. Il faut comprendre les raisons de ce comportement thérapeutique persistant et proposer des actions fermes susceptibles de le modifier, aussi bien chez l'homme que chez l'animal. Les mesures innovantes devront porter tant sur l'initiation que sur les modalités et la durée de prescription des antibiotiques et devront tirer tous les avantages du numérique en matière de conseil et d'aide à la prescription.

Il existe un faible intérêt des firmes pharmaceutiques à l'égard du développement et de la recherche sur les antibiotiques. Les causes en sont diverses : un programme de recherche et développement long et coûteux, des formalités administratives considérées comme lourdes et prolongées, une prescription des produits pendant une brève durée de mise sur le marché en raison de l'émergence rapide de résistances, un prix des produits peu élevé, une réduction des volumes de ventes par le bon usage des antibiotiques et le ciblage des modalités de prescription des antibiotiques qui doivent parfois ainsi rester des produits de niche. Il faudra proposer de nouveaux modèles originaux, avec en particulier des actions publiques/privées, pour faciliter la recherche et le développement des nouveaux antibiotiques. Il conviendra d'innover en matière de partenariat public/privé pour un modèle médico-économique attractif et propice au développement de nouvelles molécules. Vous prendrez en compte les initiatives développées au niveau européen et dans le G8 recherche.

L'utilisation des tests de diagnostic rapide revêt une importance considérable. Ces tests doivent permettre en particulier de différencier les infections bactériennes et les infections virales, évitant ainsi bon nombre de traitements antibiotiques et donner rapidement accès au diagnostic du germe en cause et à sa sensibilité aux différentes molécules antibiotiques. Les tests d'accès très facile, comme la recherche de l'antigène streptococcique dans le pharynx offerts par la CNAMTS aux médecins, sont très peu utilisés en France, ce qui est très regrettable. Des mesures innovantes doivent être proposées permettant d'accroitre l'utilisation de ces tests, dont l'évaluation des performances a déjà été réalisée. Les tests récents, comme la PCR ultra rapide devraient permettre de guider très utilement les traitements jusqu'à présent relativement empiriques. Il faut définir des modalités précises visant à accélérer leur mise en place.

Enfin, il est indispensable de proposer des objectifs chiffrés pour l'évaluation du programme, en particulier pour l'évaluation globale de la consommation des antibiotiques ou de la résistance, ainsi que pour les différentes actions proposées. Le groupe de travail pourra en tant que de besoin s'appuyer sur les avancées du Plan d'alerte sur les antibiotiques 2011-2016.

Ces propositions d'innovation devront m'être soumises pour le 30 juin 2015. Elles seront analysées en lien avec les différents ministères concernés et donneront lieu à une mise en œuvre très rapide.

Je vous remercie de votre engagement.

Marisol TOURAINE

PART ONE

« Without urgent, coordinated action by many stakeholders, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill.»

Dr Keiji Fukuda,
WHO's Assistant Director-General for Health Security,
30 April 2014

Summary

Acronyms

Institutions :

AllEnvi French National Alliance for Environmental Research

Anses French Agency for Food, Environmental and Occupational Health & Safety

ANSM French National Agency for Medicines and Health Products Safety

APUA Alliance for the Prudent Use of Antibiotics

ARS French Regional Health Agencies

AVIESAN French National Alliance for Health and Life Sciences

BPI French Public Investment Bank

CEPS Economic Committee for Health Products

CHU French Teaching Hospital

CISR Interministerial Committee for Road Safety

CMIT Academic College for Infectious and Tropical Diseases

CNAMTS French National Health Insurance Fund for Salaried Workers

CNGE National College for General Practitioner-Teachers

CRCA Regional Antimicrobial Stewardship Centre

CSA French Independent Authority to Protect Audiovisual Communication Freedom

CSF Strategic Sector Committee (Health Technologies and Industries)

CSIS Strategic Council of Health Industries

CSMF Confederation of French Medical Trade Unions

DGAL Directorate-General for Food

DGCS Directorate-General for Social Cohesion

DGOS Directorate-General for Healthcare Provision

DGS Directorate-General for Health

ECDC European Centre for Disease Prevention and Control

EFSA European Food Safety Authority

EHPAD Elderly care home

EMA European Medicines Agency

ESCMID European Society of Clinical Microbiology and Infectious Diseases

ESGAP European Study Group for Antibiotic Policies

FDA US Food and Drug Administration

FHF Hospital Federation of France

HAS French National Authority for Health

HCSP French National Council for Public Health

INPES French National Institute for Health Education and Prevention

InVS French Institute for Public Health Surveillance

MG France French Federation of General Practitioners

OMéDIT Observatories for Medicine, Medical Devices and Therapeutic Innovation

SPILF French Language Infectious Pathology Society

WHO World Health Organisation

Bacteria :

ESBLE Extended spectrum beta-lactamase-producing Enterobacteriaceae

HRB Highly-resistant bacteria

MDR Multidrug-resistant (bacteria)

MRSA Methicillin-resistant Staphylococcus aureus

PNSP Penicillin-nonsusceptible Streptococcus pneumonia

VRE Vancomycin-resistant Enterococci

VRSA Vancomycin-resistant Staphylococcus aureus

Others :

3GC Third-generation cephalosporins

ASMR Improvement in Medical Benefit

ATC Anatomical Therapeutic Chemical classification system

ATU Temporary authorisation for off-label use

CIR Research tax credit

DAM French Health Insurance Delegates

DDD Daily defined dose

DES French Specialised Degree

ECBU Cytobacteriological examination of urine

FTE Full-time equivalent

ICATB Composite index on responsible antibiotic use

JPIAMR Joint Programming Initiative on Antimicrobial Resistance

LAP Prescription-aiding software

MA Marketing authorisation

MAS Multidisciplinary Antimicrobial Stewardship (Team)

PLFSS Draft Social Security Financing Law

PROPIAS Programme for preventing hospital-acquired infections

PUI Hospital pharmacy

R&D Research & Development

RIHN Standard for innovative medical practices not listed on the general nomenclature

ROSP Payment on the basis of public health objectives

SME Small- and medium-sized enterprises

TROD Rapid diagnostic test

YIC Young innovative company

Introduction

A global situation in decline because of antibiotic overuse and misuse

Antimicrobial resistance is a natural and inescapable phenomenon that had previously been relatively limited – but it is now a proven threat for the whole of humanity. Indeed, bacterial acquisition of defence mechanisms against antibiotics calls into question the ability of healthcare systems to heal infections – even the most common. Antimicrobial resistance has been spreading to a worrying extent worldwide over the past few years and, at the same time, no antibiotic with a new mechanism of action has been developed for twenty years. **These two facts now place modern societies in an extremely vulnerable situation.**[1]

Antimicrobial resistance has already had a considerable impact on public health. According to past studies, **over 23,000 deaths are attributable every year to infections linked to resistant bacteria in Europe and the United States (US).**[2] **In France, according to the Burden study conducted by the French Institute for Public Health Surveillance (InVS), 12,500 deaths are linked to a multidrug-resistant bacterium, for 158,000 infections.** If the international community does not act, **over ten million people may die every year because of antimicrobial resistance in 2050**.

The losses in productivity generated by bacterial resistance are also high. Several studies have sought to determine the cost of resistance. **This reportedly amounts to more than EUR 1.5 billion in Europe and more than USD 55 billion in the US**[3] because of the structure of the US healthcare system. The total cost of antimicrobial resistance will exceed **USD 100 trillion by 2050 if nothing is done to tackle resistant bacteria**.[4]

Enterobacteriaceae are the most common cause of nosocomial and community-acquired infections. On the whole they are treated by antibiotics in the beta-lactam family (penicillins, broad-spectrum cephalosporins, carbapenems). But extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBLE) have been spreading rapidly over the past decade or so, in the community and the hospital sector, particularly in the cases of *Escherichia coli* and *Klebsiella pneumoniae*.

Today, 10% of *Escherichia coli* and more than 30% of *Klebsiella pneumoniae* are resistant to Third-Generation Cephalosporins (3GC).[5] In concrete terms, out of ten patients infected by these infectious agents, contracted at home or in a care environment, between one and three of them may not respond to the conventional treatments available to community healthcare staff.

To treat such infections, it is sometimes necessary to hospitalise patients so that they can be given carbapenems, a class of antibiotics administered entirely intravenously. But carbapenems are not a viable long-term solution since they should only be used to treat infections caused by nosocomial bacteria, which are particularly resistant to common antibiotics. Indeed, they are largely involved in the occurrence of antimicrobial resistance in hospitals. It seems only logical, therefore, that carbapenem-resistant bacteria can now be observed – particularly *Klebsiella*.[6]

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1 Laxminarayan R, Duse A, Wattal C. Antibiotic resistance. The need for global solutions. Lancet Infect Dis 2013;13:1057-98

2 https://www.google.fr/search?q=ecdc+the+bacterial+challenge,+time+to+react&ie=utf-8&oe=utf-9&gws rd=cr&ei=XrptVbz5OMGBU9v-glgJ

3 Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States 2013 (http://www.cdc.gov/drugresistance/threat-report-2013/)

4 (http://domino.home/html/home.html?target=www.rand.org/randeurope/research/projects/antimicrobial-resistance-costs.html

5 Ears-Net database. http://ecdc.europa.eu

6 Nordmann P, Poirel L. The-difficult-to-control spread of carbapenemase producers among Enterobacteriacae worldwide. Clin Microbiol Infect 2014; 20:821_30

Although this phenomenon is still relatively limited in France, it is spreading very quickly particularly in Greece, Italy, the Middle East, India, Asia and North Africa. The risk of cases of Highly or even Totally Resistant Bacteria cases being imported by patients or tourists could mean that **the French healthcare system is no longer able to treat a certain number of patients.** The rise in the number of resistant bacteria could shift the balance in the environmental bacterial flora in a dangerous and durable way. **Without the appropriate treatments to hand, the human and financial costs in such a situation will be disastrous.**

Investment in antibiotics has slumped over the past ten years or so, for manufacturers consider the return on investment to be too low because of unappealing sales prices, a short treatment duration and a reduction in the number of prescriptions in the context of antimicrobial stewardship programmes. **As a result, few new antibiotics have been placed on the market in recent years, and precious few are currently being developed.**

If this situation continues, human societies may return to a world without antibiotics – turning the clock back 70 years – with worse effects on the healthcare system than if antibiotics had never existed. The consequences for modern clinical medicine would be dramatic, since complex surgery, high-infectious-risk treatments, organ transplants, newborn and intensive care would become impossible as the risks are too high. **Antibiotic resistance is therefore endangering our way of life as we know it, head-on and in a global manner, over the short term, and is indirectly compromising other medical breakthroughs that have already been made.**

As a country, France continues to overuse antibiotics

As a pioneer in research on antibiotics and the fight against antimicrobial resistance, France has set up several plans since the early 2000s in an attempt to reduce antibiotic use. For, **still today and in spite of the progress made between 2002 and 2005, France consumes 30% more antibiotics than the European average, and almost three times more than the Netherlands, Sweden and Norway.** According to the French National Agency for Medicines and Health Products Safety (ANSM), **this overuse represents an additional expense of between EUR 71 million (compared with the European average) and EUR 441 million (compared with the most virtuous European countries).**

As such, **in 2013, 97.6 million packs of antibiotics were reimbursed by the French Health Insurance System** (+0.2% compared with 2012). And yet, **between 30 and 50% of antibiotic treatments are prescribed unnecessarily in France**, either in the community, elderly care homes (EHPADs) or hospitals, particularly for primarily viral infections of the airways (rhinopharyngitis or the common cold, sore throat, sinusitis, ear infection and bronchitis). Rapid diagnostic tests even exist for some illnesses, but too little use is made of them. **Only 30% of GPs report using Rapid Diagnostic Tests (TRODs) for sore throats.** This meant that **28.3% of French patients were treated with antibiotics in 2013.** Such treatments are also often extended with no re-examination. Antibiotics are likely to be unnecessarily prescribed in some living environments, elderly care homes in particular, for urinary tract infections with no clinical signs and for bronchitis.

After stabilising between 2005 and 2010, French antibiotic consumption has been climbing again by a few percent every year – in the community and the hospital sector alike.[7] Accordingly, in outpatient medicine, average consumption within the European Union (EU) was 21.5 Daily Defined Doses (DDDs) per 1,000 inhabitants per day in 2012, compared with 29.7 DDDs for France.[8] **In 2013, France was the second largest consumer in Europe (30.14 DDD), just behind Greece (32.24 DDD).** For inpatient medicine, **France is in seventh place with a consumption of 2.17 DDD per 1,000 inhabitants per day in 2013.** The reasons for such therapeutic consumption patterns are not clear. **There is a cultural phenomenon regarding health product** – and particularly antibiotic – **consumption in France** that differs from other countries like the Netherlands, Scandinavian countries and Germany, in which antibiotic treatments are used with much greater care.

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[7] ANSM Nov 2014 Evolution des consommations antbiotiques en France entre 2000 et 2013

8 Esac-Net. Database http://ecdc.europa.eu

In 2010, France was also the largest consumer of antibiotics in agriculture, tied with the Netherlands. Recent data (2014) shows that both of these countries have considerably cut down on their use of antibiotics in the animal sectors. Now, they consume less than Belgium, Germany, Spain, Italy, Hungary, Portugal and Cyprus.[9] The tonnage of antibiotic treatments in animals in France, which remained constant between 1999 and 2007, fell between 2008 and 2013. Moreover, **two years after being set up in France, the EcoAntibio Plan further enabled antibiotic consumption to be reduced significantly, with a 12.5% drop in animal exposure between 2012 and 2014.**[10] This decrease varies between animal sectors, with a very sharp drop in pigs, but more steady in cattle.

The fact that antibiotics are present across the board of human activity has an influence on the presence of resistant bacteria in the environment. Few standards govern household waste, hospital activity, livestock holdings or manure spreading near waterways, and yet they expose the whole environment to antibiotics. We still know very little about the actual effect on humans of antibiotic traces found in the environment, but they **very likely foster the development of resistance that has until now been primarily observed in human and animal medicine.**

For all that, the situation is not all bad in terms of antimicrobial resistance in France. While some countries, such as the United States and Ireland, have seen a rapid rise in the prevalence of Vancomycin-resistant Enterococci (VRE)[11], this is limited to a few controllable epidemic phenomena in France. Moreover, **thanks to such hygiene policies as rubbing hands with hydroalcoholic solutions, the prevalence of Methicillin-resistant Staphylococcus aureus (MRSA) has halved in 15 years.** Lastly, the number of colitis cases linked to *Clostridium difficile* remains relatively limited in France compared with other countries, such as the United States.

France has excellent bacterial resistance and antibiotic consumption monitoring networks. Likewise, there are indicators on hygiene and responsible antibiotic use available in hospitals (ICATB, the scoreboard for nosocomial infections) which are accessible to everyone. The French National Authority for Health (HAS), which certifies healthcare entities, collects these indicators which represent major, particularly valued criteria.

Act now, all together, to tackle antimicrobial resistance

Antimicrobial resistance is a global phenomenon that has been picking up pace since the turn of the new millennium. It is striking to note that this period corresponded to the end of patents for a great many antibiotics and the marketing of inexpensive generic versions. This situation probably made new uses of such medicines possible in a great many countries, both in human medicine and in livestock, which has played a part in increasing the presence of antibiotics in the environment.

All living beings are now surrounded by resistant bacteria. Water, soil, food and human activity contribute to the selection of resistance by their multiple pollution types. The presence of antibiotics in all reservoirs of life calls for global action, for the good of human, animal and environmental health. Without it, the occurrence and spread of bacterial resistance will only increase – with a considerable impact in all human societies**. Action is therefore necessary at global level, with account taken of the specific situations in different countries and the global nature of the problem, well beyond the use of antibiotics.**

Measures have already been underway for several years, but unequally across the different regions of the world. For example, few countries (EU member states, Australia) prohibit the use of antibiotics as growth factors in animals. This form of misuse has been banned in Europe since 2006, though **the treatment of entire farms in "metaphylaxis" is still widespread in some EU member states.**

9 Grave K, Torren-Edo J, Muller A et al. Variations in the sales and sales patterns of veterinary antibacterial agents in 25 European countries. J Antimicrob Chemother 2014, 69:2284-2291
10 Plan Ecoantibio http://agriculture.gouv.fr/plan-ecoantibio-2017
11 Ears-Net database. http://ecdc.europa.eu

Given this global threat, several national and international agencies have included antimicrobial resistance on their list of priorities over recent years. Accordingly, **on 26 May 2015, the World Health Organisation (WHO) adopted a global action plan to tackle antimicrobial resistance.**[12] In the same way, governments are taking action worldwide in the understanding that swift action is essential. For the first time, a **five-year (2016-2020) strategy in the United States aims at significantly increasing the amount of federal funding for combating and preventing antibiotic resistance, with a budget of USD 1.2 billion – double the budget to date.**[13] Furthermore, **the UK has announced the creation of a fund – the Fleming Fund – of GBP 195 million aimed at setting up a global epidemic surveillance network and at building capacity to address epidemics in low- and middle-income countries.** The British working group goes as far as recommending the setup of a global fund for tackling antimicrobial resistance by supporting the development of pharmaceutical group projects.[14]

Ideas for tackling bacterial resistance should also soon be forthcoming from other countries such as Germany and Canada. However, beyond the measures adopted by each State, **only the adoption of a global strategy and joint specific action through international conferences, like the G7 or G20, will enable antimicrobial resistance to be tackled, via a comprehensive approach that encompasses humans, animals and the environment.** Indeed, only a "One Health" initiative will enable bacterial resistance to be curbed effectively. **Given the dynamics of antimicrobial resistance, overlooking any reservoir of life would render any action futile in the long-term.**

Antibiotics are specific types of drug because of their target and their collective impact on health. **And yet their use has become widespread and human society has been unable to protect this precious resource.**[15] Against bacteria that are constantly able to develop new mechanisms of resistance, **we must not only control infections, but also learn to live in harmony with microbial flora.** This places us in a new relationship with our environment.

With the end of the "miracle of antibiotics" nigh, understanding the phenomenon of antimicrobial resistance in its entirety is vital. While it is necessary to support the development of new health strategies, it is above all crucial that the prescription, consumption and management of existing therapies – particularly regarding their disposal in the environment – be improved. **Beyond having to find new ways of treating resistant infections, it is also time to learn how to prevent them.** The promotion of hygiene and that of vaccination are also priorities in the fight against antimicrobial resistance.

12 http://apps.who.int/gb/ebwha/pdf files/WHA68/A68 R7-fr.pdf
13 https://mail.google.com/mail/u/0/#inbox/14c5b8d0392202c0
14 http://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20%GENERATIONS%20FINAL%20WEB0.pdf
15 Carlet J, Collignon P, Goldmann D et al. Society's failure to protect a precious resource: antibiotics. Lancet 2011;378:369-71

Presentation of the special working group

Set up on 26 January 2015, the special working group for keeping antibiotics effective was asked to **come up with innovative, concrete and practicable proposals which must help to reduce antibiotic consumption in France by a quarter by the end of 2016.** Three priority areas have been highlighted in the engagement letter:

- **Communication and information,** particularly for the general public
- Healthcare professionals' **prescribing behaviours**
- **Appeal particularly in terms of industrial research** for the development of new antibiotics or new therapeutic strategies and new diagnostic methods

Initially comprising fifty qualified experts (researchers, healthcare professionals, administrators, manufacturers), **the working group and its sub-groups ended up bringing together more than 120 experts committed to tackling antimicrobial resistance.**

Five multidisciplinary working groups were set up to put forward specific measures in each priority area:

- The "**Cost of antimicrobial resistance**" group, coordinated by Bruno Coignard (InVS) was asked to **come up with a method for calculating the human and economic cost of bacterial resistance**. Two studies conducted by the ANSM and InVS have provided quantitative data on the phenomenon of bacterial resistance in France.

- The "Responsible antibiotic use" group, coordinated by Céline Pulcini (Nancy Teaching Hospital), came up with proposals for improving healthcare professionals' training on antimicrobial resistance, reducing antibiotic consumption, improving the quality of community and hospital prescriptions and presenting indicators for responsible antibiotic use. The group's methodological approach particularly looked at dialogue between patients and their doctors in order to improve professional communication on antimicrobial resistance.

- The "Communication, Information and Education" group, coordinated by Claude Rambaud (Ciss) outlined objectives for a future information campaign and suggested a range of innovative tools for getting each and every citizen involved in keeping antibiotics effective. These measures have the long term in mind and are aimed at improving overall knowledge on antimicrobial resistance.

- The "**Research, innovation and new medico-economic models**" group, coordinated by Florence Séjourné (Da Volterra), brought together various research and industry stakeholders so as to **come up with a set of measures for establishing a single continuum for antibiotics**. The group also put forward **proposals for supporting cross-cutting research on antibiotics, particularly in social sciences and economics, to gain an overall understanding of antimicrobial resistance.**

- The "**Antimicrobial resistance and the environment**" group, coordinated by Antoine Andremont (University of Paris-Diderot) and Gilles Pipien (French Ministry for the Environment), was set up to make use of ongoing projects on the relationship between human activities, antibiotics, the environment and antimicrobial resistance. It set out measures that should **bring the barriers down between measures aimed at tackling antimicrobial resistance, in all human activities**.

The working group's recommendations

At the end of the various working groups' discussions, **four major prerequisites were identified if antibiotics are to remain effective.** These guidelines go hand in hand with **the creation of four cross-cutting tools that are necessary for setting up the measures advocated in this report.**

The working groups outlined four operational objectives for effectively tackling antimicrobial resistance. Each one includes a list of recommendations for the measures to be set up. These are given in more detail in Part Two of this report:

Objective 1: Adopt a national strategy in favour of research on antimicrobial resistance and the development of innovative products that tackle antimicrobial resistance

- Set up a national five-year research programme on antimicrobial resistance, coordinated by the research alliances – **page 57**;
- Secure funding for the research programme over five years – **page 59**;
- Make the development of innovative products more effective to remove obstacles and speed up the process leading to marketing – **page 65**;
- Restore value in the equation of the medico-economic model for products that tackle bacterial resistance by reducing their Research & Development (R&D) cost, by setting up an extension of market exclusivity on such products in Europe and by revising the systems by which their prices are set – **page 68.**

Objective 2: Propose a set of indicators for measuring and observing antimicrobial resistance and its cost over time, in the different sectors (human, animal and environmental)

- Establish medico-economic indicators on antimicrobial resistance throughout the healthcare system – **page 33**;
- Foster the emergence of indicators on the cost of bacterial resistance in the animal world by setting up a veterinary multidisciplinary group – **page 33**;
- Strengthen and coordinate the surveillance networks for bacterial resistance and antibiotic consumption – **page 33**;
- Foster the setup of workshop sites coordinated by a national observatory on bacterial resistance in the environment, so as to standardise the markers by which the level of antimicrobial resistance in the different reservoirs of life can be measured in relation with the diverse uses made of antibiotics – **page 74.**

Objective 3: Improve responsible use of antibiotics by funding prescription support structures, providing prescribers with a set of teaching aids and increasing personal and collective professional accountability

- Finance multidisciplinary teams (with leading infectious diseases advisors) in healthcare entities and Regional Antimicrobial Stewardship Centres (CRCAs) in outpatient medicine – **page 39**;
- Increase the number of points allocated to responsible antibiotic use in the Payment on the basis of public health objectives (ROSP) scheme – **page 40**;
- Publish and harmonise national recommendations on antibiotic treatment – **page 41**;
- Limit the duration of the first prescribed course of antibiotics to 7 days – **page 41**;
- Provide prescribers with a "communication pack" containing a public commitment charter on responsible antibiotic use (including in veterinary medicine), specific prescriptions and non-prescription of a course of antibiotics, as well as factsheets on antimicrobial resistance – **page 42**;
- Improve initial training and continuing education of healthcare professionals (including for vets and stockbreeders) – **page 42**;
- Step up support measures for "big prescribers" through targeted action plans (including in veterinary medicine) – **page 40**;
- Produce new indicators for monitoring responsible use in healthcare entities and elderly care homes – **page 41**.

Objective 4: Raise public awareness of antimicrobial resistance through targeted local and national initiatives that have a long-term outlook

- Commission the CNAMTS, in partnership with other stakeholders, to organise a large-scale information campaign – **page 51**;
- Set up an online institutional portal on antimicrobial resistance where each section of the public can find the right information – **page 48**;
- Support initiatives for the general public and professionals in favour of keeping antibiotics effective – **page 52**;
- Raise public awareness of careful, sustainable use of disinfectants and biocides – page 74;
- Include antimicrobial resistance in all educative programmes and create new cross-disciplinary university courses on antimicrobial resistance – **page 53**;
- Finance interactive teaching aids, especially e-Bug, and knowledge-sharing tools – **page 53.**

4 cross-cutting tools for carrying out and coordinating the recommendations

Cross-cutting tools are essential to be able to put the various recommendations into practice:

Tool 1. Set up an Interministerial Committee in charge of antimicrobial resistance

Resistance to anti-infectious agents is a global problem in which a great many structures are involved – particularly ministries for health, agriculture, the environment, research, higher education and industry. Whereas coordination is absolutely essential, many projects and funds are implemented with no structural cohesion. The working group recommends setting up an interministerial committee under the French Prime Minister, which is coordinated by an interministerial delegate in charge of antimicrobial resistance, in the same way as the Interministerial Committee for Road Safety. This new committee must wield the necessary remit and powers for seeing through the actions set out in this report. Its purpose is to create synergies by breaking down the barriers between the separate initiatives on bacterial resistance, and to shed greater clarity on the measures taken by the different agencies, ministries, scientific or professional associations and societies. The interministerial delegate in charge of antimicrobial resistance will be responsible for coordinating all of the measures adopted by the Committee in close liaison with the various stakeholder members. He will also have to coordinate or co-coordinate the different groups that will be set up to oversee all of the teams dedicated to tackling antimicrobial resistance.

Tool 2. Allocate and secure over five years the necessary resources for setting up a National Intersectoral Research and Innovation Plan on Antimicrobial Resistance

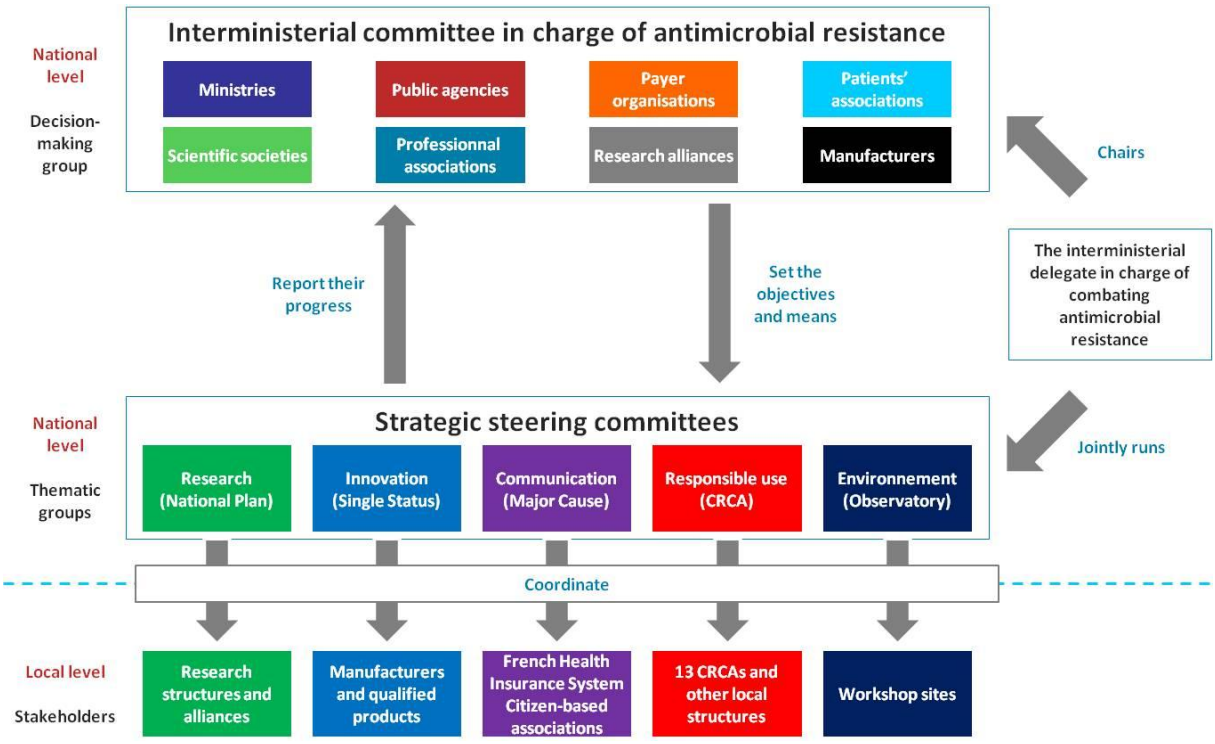
The discovery of anti-infectives, and antibiotics in particular, was an extraordinary breakthrough that has made it possible to extend human life spans – beyond all expectations. The paradigm is that this tremendous invention has fallen victim to its own success: antibiotic resistance is steadily becoming a major public health problem for France and the whole world. And yet, compared with other major health risks (cancer, HIV or hepatitis for example), there is a lack of cohesion in research funding and programmes dedicated to antimicrobial resistance. What's more, the research networks are not structured. The working group therefore recommends that all issues bearing upon antibiotic resistance (emergence, transmission, monitoring, responsible use, therapies, indicators, social and economic aspects) be addressed through a National Intersectoral Plan. This would particularly aim at improving the visibility of research stakeholders (public and private) in France and of research programmes. This research programme would be financed over five years (2016-2020) by the different financial stakeholders, including public-private partnerships, on the basis of a framework research programme for tackling bacterial resistance. It would be coordinated by the interministerial cell, as well as a scientific committee made up of international and national experts renowned for their high-quality research. Lastly, it will have to fit squarely into the context of the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) in which France is involved.

Tool 3. Create a special status for innovative products that tackle antimicrobial resistance

The dearth of innovation in antibiotic treatments can be explained by the low economic prospects for manufacturers. Indeed, the unique dynamics of this area sets it apart from others, in that the use of new therapies should be limited to keep them effective. This does not enable sufficient return on investment according to the traditional idea of profitability, which is based on sales volumes. The working group therefore recommends that innovative products aimed at tackling antimicrobial resistance – covering at once therapeutic, preventive and diagnostic strategies – become products endowed with a special status. This status should involve a series of concomitant incentive measures that are to accompany the product at each stage of its development, and to offer sufficient return on investment with greater predictability for the company. A European initiative should be undertaken to encourage research and development in new products that tackle antimicrobial resistance.

Tool 4. Declare the fight against antimicrobial resistance a "2016 Major National Cause"

Antibiotics are precious drugs that must be protected, through a sustainable development policy. And yet the use of these "miracle drugs" has become commonplace, and it is therefore vital to highlight the need to keep them effective. As part of a major national information campaign, the working group recommends labelling the "fight against antimicrobial resistance" as a "2016 Major National Cause". Every year, the French Prime Minister attributes this governmental label to a public interest campaign on a given theme, and launches a call for tenders to which associations committed to the cause can respond. In addition to shedding light on the work carried out by such organisations, this label allows for free-of-charge broadcasting of public television and radio messages.



A set of indicators for assessing the effectiveness of the recommended measures

For each objective, **indicators have been proposed for assessing the effectiveness over time of the working group's recommendations**. Together, they aim at demonstrating, in the medium term, that the social and economic benefits observed have largely justified the cost of the measures set up. **In 2017, the working group recommends that the interministerial cell on antimicrobial resistance publish a report on how these measures are progressing.**

Objective	Indicator	Target for 2020	Data source
1	• Number of research projects funded • Number of projects for clinical trials of qualified products • Number of research projects on old antibiotics • Number of research projects on antimicrobial resistance and the environment		French Research Ministry
	• Number of qualified products under development on French soil • Number of antibiotics with an ATU (temporary authorisation for off-label use) • Number of new products placed on the market		ANSM
	• Industrial R&D amount reported in France dedicated to anti-infectives that tackle antimicrobial resistance		French Industry Ministry
	• Variation in antibiotics prices in France	Less than 1%	CEPS
2	• Variation in antibiotics consumption	Fall by 25%	ANSM / CNAMTS
	Maintain a low level of resistance • % of Escherichia coli resistance to 3GC • % of Klebsiella pneumoniae resistance to carbapenems • % of methicillin resistance in Staphylococcus aureus	• Less than 10% • Less than 1.5% • Less than 15%	InVS / Onerba ECDC
	• Number of publicly funded medico-economic projects	-	French Research and Health Ministry

Objective	Indicator	Target for 2020	Data source
3	• Number of regions with an operational CRCA (incl. number of FTE)	Cible : 14 (dont Outre-Mer)	ARS
	• Number of antimicrobial stewardship advisor FTEs set up in hospitals	Cible : 840	French Health Ministry
	• % of hospitals with an ICATB equal to 0 • % of elderly care homes with an ICATB equal to 0	• Less than 5% • Less than 10%	French Health Ministry
	• % of courses of antibiotics prescribed for longer than 7 days in the community sector	Less than 10%	CNAMTS (from healthcare information systems)
	• % of <u>unjustified</u> curative antibiotic treatments in hospitals lasting more than 7 days	Less than 10%	French Health Ministry
	• % of prescribers signing and displaying a public commitment charter • % of hospitals signing and displaying a public commitment charter	• More than 80% • More than 90%	Professionals organisations and associations (community sector) + French Health Ministry FHF (hospital sector)
	• % of professionals (all sectors) trained in antibiotic treatments in the past 3 years (frequency to be defined depending on speciality)	More than 80%	CNAMTS Ordres professionnels
	• Availability of national recommendations on first-line antibiotic treatments in the main clinical situations (with treatment durations minus ranges), updated in the past 4 years	-	HAS / HCSP
4	• Number of visits to the portal in the past year • Number of downloads from the portal in the past year	• More than 1 million • More than 500,000	French Health Ministry
	• % of the population knowledgeable about antimicrobial resistance • % of the population subscribing to the campaign's messages	More than 90%	CNAMTS (survey)
	• Number of visits to the e-bug website	30% increase	E-Bug
	• % of students with specific knowledge of antimicrobial resistance • % of Earth and Life Science teachers with specific knowledge about antimicrobial resistance	• More than 90% • More than 95%	French National Education Ministry (survey)
	• Number of projects aimed at citizens		French Health Ministry
	• Number of audiovisual products on antimicrobial resistance		CSA

PART TWO

« Effective antibiotics have been one of the pillars allowing us to live longer, live healthier, and benefit from modern medicine. Unless we take significant actions to improve efforts to prevent infections and also change how we produce, prescribe and use antibiotics, the world will lose more and more of these global public health goods and the implications will be devastating. »

Dr Keiji Fukuda,
WHO's Assistant Director for Health Security,
30 April 2014

The cost of antimicrobial resistance

The "Cost of antibiotic overuse and resistance", coordinated by Bruno Coignard (InVS), was tasked with providing information about the cost of antibiotic overuse and resistance, particularly within France, so as to provide food for thought for the other working groups. It brought together 19 experts and representatives from the agencies and ministries concerned. This group met four times between February and May 2015.

In the time it had been given, the group carried out three different research activities:

- A literature review (non-systematic), giving precedence to the most recent studies and review papers published abroad on the subject;
- Two original studies, based on the most recent French findings available on antibiotic consumption and antibiotic resistance in human health, conducted by the ANSM and InVS respectively;

Formulation of recommendations aimed at promoting additional work, particularly the reproduction of the two aforementioned studies in veterinary medicine, in liaison with the French Agency for Food, Environmental and Occupational Health & Safety (Anses).

An underestimated cost of antimicrobial resistance

Although the dangers of increasing antimicrobial resistance are widely acknowledged, in an article published in 2013[16] two English health economists asked why action aimed at limiting its spread had come too little or too late. One of their hypotheses concerned evidence-based policy making, which prioritises health problems by economic burden and cost effectiveness of interventions. They then observed that health economists had been "**unable to show that antibiotic resistance costs enough to be a health priority**".

In 2001, these authors conducted a systematic literature review for WHO[17], which highlighted **the severe lack of work on the cost of resistance**. Updated in 2012 for the UK Department of Health[18], this study highlighted the progress made on the subject in 10 years. And yet, **the additional cost estimated for a resistant bacterial infection could vary from USD 5 to 55,000 depending on the study and bacteria studied.** The quality of the work selected for analysis was not questioned, but these only partially studied the cost of resistance by focusing solely on some bacteria or types of infection. **The evaluated costs were limited to the additional cost incurred by the treatment or the mortality linked to a resistant bacterial infection.** Lastly, most of these studies were conducted in the United States.

A recent article summed up the current limits of the studies available. **First of all, there are the usual problems to do with their quality**: no adjustment across several factors, including the length of hospitalisation prior to the infection, patient comorbidity and susceptibility or the suitability or otherwise of an empirical antibiotic treatment. Moreover, its authors stress that the wide variability in the costs evaluated is currently associated with the heterogeneity and size of the populations being studied, the choice of control groups or the choice of infectious sites and pathogens. This article also recalls **the difficulties surrounding the variable definitions of antibiotic resistance, or patient follow-up periods that are not long enough**. Finally, it outlines the limits of studies that do not combine several perspectives: those of the patient and his/her insurance company for treating the infection, those of the hospital regarding the measures set up to control resistant bacteria, and those of society in terms of productivity losses[19]. **A number of additional studies are therefore necessary to evaluate the cost of resistance to antibiotics**.

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[16] Smith R, Coast J. The true cost of antimicrobial resistance. BMJ 2013;346:f1493

[17] Smith RD, Coast J, Millar MR, Wilton P, Karcher A-M. Interventions against anti-microbial resistance: a review of the literature and exploration of modelling cost-effectiveness. WHO, 2001.

[18] Smith R, Coast J. The economic burden of antimicrobial resistance. Why it is more serious than current studies suggest. 2013. Available at http://lshtm.ac.uk/php/economics/assets/dh_amr_report.pdf

[19] Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? Clin Microbiol Infect 2014;20(10):973-80

The complex problem of evaluating the cost of antibiotic resistance

Antibiotic resistance is an acknowledged public health problem today, and there is a plethora of surveillance data available. However, it is a very broad nosological phenomenon. Antimicrobial resistance encompasses multiple bacteria and several types of infection, from the most benign to the most severe. In the same way, it covers many different characteristics of resistance to the different antibiotics available for human and animal treatments.

There are two categories of bacterial resistance. Natural resistance corresponds to certain bacteria that resist antibiotics in an innate manner. This is a marker of the bacterium's identity. The second category corresponds to acquired resistance. This concerns bacteria which, via genetic modifications, escape the action of antibiotics to which they are usually susceptible. This is an epidemiological marker and is the main target of existing surveillance networks. Such epidemiological markers can be studied separately or together. **They make it possible to define Multidrug-Resistant (MDR) Bacteria, i.e. which are able to develop resistance to several families of antibiotics.**

But for all that, the definition of MDR bacteria is not subject to international consensus today. This led to the European Centre for Disease Prevention and Control (ECDC) making proposals on the subject in 2011. **According to this Centre, an MDR bacterium is an isolate which is non-susceptible to at least 1 agent in at least 3 different antimicrobial categories (these categories can vary from one isolate to another).**[20]

The scope and complexity of the "resistance" phenomenon explains why it has long been difficult to sum up its scope in a few intelligible and easy-to-communicate figures. The few studies addressing the subject in an overall manner are summarised below.

Evaluation of the medical and societal costs of antibiotic resistance

Two studies abroad have endeavoured to put a global cost on antibiotic resistance for the healthcare system (cost of patient care) and for society (productivity losses of the individuals affected). The first was published in 2009 by the ECDC[21]. **This estimated that around 386,000 MDR bacterial infections arise every year in Europe and 25,000 deaths result from these infections. Their societal cost was estimated to be EUR 1.5 billion per year: 910 million associated with patient care and 600 million associated with productivity losses of the patients infected** (absence from work or premature deaths). A panel of five bacteria (nine isolate-antibiotic pairs) were taken into account:

- Methicillin-resistant *Staphylococcus aureus*
- Vancomycin-resistant *Staphylococcus aureus*
- Vancomycin-resistant Enterococci
- Penicillin-nonsusceptible *Streptococcus pneumoniae*
- Third-generation cephalosporin (3GC) or carbapenem-resistant *Escherichia coli*
- C3G or carbapenem-resistant *Klebsiella pneumoniae*
- Carbapenem-resistant *Pseudomonas aeruginosa*

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20 Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81

21 ECDC and EMEA. The bacterial challenge : time to react. ECDC, 2009, report, 54 p. Available at: http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_To_React.pdf

The data used was the European Antimicrobial Resistance Surveillance Network (EARS-Net) data from 2007. **This was extrapolated to other infectious sites to which attributable mortality ratios from the literature were applied**. The societal cost was evaluated by adding together the costs associated with patient care (in the hospital and community sectors) and those associated with productivity losses (loss of earnings for the patients concerned). **Given that the surveillance data used for this study is out-of-date and that considerable changes in the epidemiology of antibiotic resistance in Europe have been observed since this date,[22] it would be worth updating this estimate.**

The second, more recent study was published by the US Centers for Disease Control and Prevention (CDC) in 2013. This made use of North American surveillance data collected between 2009 and 2011.[23] The reference panel was wider, considering 17 isolate-antibiotic pairs, adding several bacteria to the panel used by the ECDC such as *Neisseria gonorrhoeae*, Groups A and B Streptococci, *Acinetobacter, Salmonella, Shigella, Campylobacter, Mycobacterium tuberculosis, Clostridium difficile* and even a fungus (*Candida*). **This report estimated that more than 2 million patients are infected every year in the US, and that 23,000 die as a result.** *C. difficile* is not, strictly speaking, a resistant or multidrug-resistant bacterium, but the diarrhoea it causes often occurs after antibiotics have been taken. **The CDC therefore added 250,000 cases of infection by *C. difficile*, including 14,000 deaths, to the previous estimates.**

Lastly, the CDC report referred to an estimate reached by the Alliance for Prudent Use of Antibiotics (APUA), an international non-governmental organisation. **In 2010, this put the annual cost of resistance in the US at around USD 55 billion, USD 20 billion of which was linked to patient care and USD 35 billion to productivity losses**.[24] This estimate was nevertheless based on a single-centre study conducted in Chicago in the late 2000s, which prompts some authors to put its scope into perspective.[25] Finally, the epidemiology of resistance in the US is very different to that observed in France and Europe and, as such, **the practical scope of these estimates for France is limited.**

Despite the fact that the data used is out-of-date and the epidemiological situation in the US is very specific, the public health and economic cost estimates given in both of these studies are still significant and justify the actions being taken on the subject in Europe and North America over recent years. But these studies do underestimate the actual cost of overall antibiotic resistance for all that, because they are restricted to a handful of pathogens, primarily MDR bacteria, and only assess the economic consequences of such infections in terms of medical treatment (in hospitals and in the community) and productivity losses for the infected, or deceased, patients. **Other costs are not factored in as a result, such as those linked to the measures set up in healthcare entities to control the spread of resistant bacteria.**

This all means that even the most significant estimates reached to date in terms of the cost of resistance do not allow for antibiotic resistance to be ranked as a top public health priority. Regarding the US, the APUA's estimate ranks antimicrobial resistance in 10th place of the nation's public health priorities, behind nine other pathologies including cardiovascular diseases, road traffic accidents, cancer, mental disorders, Alzheimer's and diabetes.[26]

22 ECDC. Antimicrobial resistance surveillance in Europe 2013. ECDC, 2014, report, 211 p. Available at http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/

23 Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States, 2013. CDC, 2013, report, 114 p. Available at http://www.cdc.gov/drugresistance/threat-report-2013/

24 Alliance for the Prudent Use of Antibiotics (APUA). The cost of antibiotic resistance to U.S. families and the health care system. Available at http://www.tufts.edu/med/apua/consumers/personal_home_5_1451036133.pdf

25 Smith R, Coast J. The economic burden of antimicrobial resistance. Why it is more serious than current studies suggest. 2013. Available at http://lshtm.ac.uk/php/economics/assets/dh_amr_report.pdf

26 Smith R, Coast J. The true cost of antimicrobial resistance. BMJ 2013;346:f1493

The interest of macroeconomic studies

Not one of the previous studies undertaken takes a global approach to measuring the cost of antibiotic resistance. And neither do they combine other scenarios, including that of **a world in which there would not be a single effective antibiotic left for treating the most vulnerable patients, exposed to ever more complex medical procedures**. Further research is therefore vital to factor in not just the costs associated with returning to an age before antibiotics – which has already been measured by existing studies – but also those associated with giving up the progress made in modern medicine – which still needs evaluating.

For example, several authors feel it would be worthwhile estimating the costs associated with a rise in postoperative infection rates in joint replacement orthopaedic surgery, due to ineffective antibiotic prophylaxis in surgery, or the costs associated with patients refusing to undergo surgery for fear of the possible infection-related complications. **Today, less than 2% of patients develop an infection following hip replacement surgery. Tomorrow, these surgical site infections may, without any effective antibiotics, concern 40-50% of patients operated, 30% of whom would not recover from their infection**. Patients refusing to undergo surgery would see their life expectancy or quality of life diminish, generating potentially significant productivity losses for society. The same reasoning can be applied to several other complex surgical or medical procedures (organ transplants, cancer treatment, intensive care for newborns, etc.), which are now commonplace. **Beyond these consequences for patient health, there is also therefore the potential that antibiotic resistance will affect numerous aspects of our health economy today.**

In 2014, as part of the "Review on Antimicrobial Resistance" project set up in the UK by the British Prime Minister and the Wellcome Trust,[27] two macroeconomic prospective studies were carried out, taking a more global approach. With the help of scenarios, these set out to assess the consequences of anti-infective resistance worldwide by 2050. Their approach is innovative but the estimates are still only partial for at least two reasons. One, they only looked at six pathogens: *Klebsiella pneumoniae, Escherichia coli, Staphylococcus aereus, Mycobacterium tuberculosis* (tuberculosis), *Plasmodium spp* (malaria) and HIV. Two, they only assessed the impact of these infections on nations' Gross Domestic Product (GDP), in terms of impact on their labour force and on economic trade. They did not therefore look at their societal or medical costs.

The first study, conducted by RAND Europe, used 8 scenarios based on several hypotheses: total resistance of the pathogens studied (not a single effective anti-infective left), constant infection rates and rising increase in the proportion of totally resistant pathogens until 2050 (varying depending on scenario between current proportions staying the same and 100% of totally resistant pathogens). **The fall in the world's population as a result of these 8 scenarios varied between 11 and 444 million inhabitants. The estimated cost for the global economy ranged from USD 2 to 125 trillion. The largest impact was measured in Eurasia and Africa**.[28]

The second study, conducted by KPMG, used 4 scenarios based on different hypotheses: resistance to first-line anti-infectives only, constant or doubled rates of infection, and variable increase in the proportion of resistant pathogens (+40% or 100%). **The fall in the world's population as a result of these 4 scenarios was 700 million inhabitants. The estimated cost for the global economy was put at USD 14 trillion. The largest impact was measured in African countries[29].**

Although the hypotheses adopted for these prospective studies can be debated, the costs are still breathtaking irrespective of the scenario considered. Based on both of these studies, the "Review on Antimicrobial Resistance" concluded that, worldwide, if we fail to act on antimicrobial resistance[30], then an additional 10 million lives would be lost each year by 2050, at a cost to the world economy of more than USD 100 trillion.

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27 The Review on Antimicrobial Resistance. Available at http://amr-review.org/

28 RAND Europe. Estimating the economic costs of antimicrobial resistance. Model and results. Rand Europe, 2014, report, 113 p. Available at: http://www.rand.org/pubs/research reports/RR911.html

29 KPMG. The global economic impact of antimicrobial resistance. KPMG LLP, 2014, report, 44 p. Available at https://www.kpmg.com/UK/en/IssuesAndInsights/ArticlesPublications/Documents/PDF/Issues%20and%20Insights/amr-report-final.pdf

30 The Review on Antimicrobial Resistance. Tackling a crisis for the health and wealth of nations. The Review on Antmicrobial Resistance, 2014, report, 20 p. Available at: http://amr-review.org/

Two original studies conducted in France for obtaining national estimates

In France, national surveillance of antibiotic resistance is coordinated by the InVS.[31] The ANSM is in charge of monitoring antibiotic consumption.[32] Based on networks in which various partners are involved, there is an enormous amount of surveillance data available. What's more, since the early 2000s, these networks provide useful data to healthcare professionals for adapting the prescription recommendations, or to public policymakers. But for all that, the product indicators (effect of a MDR bacterium per 1,000 bed-days, antibiotic consumption in daily defined doses per 1,000 inhabitants per day, etc.) are difficult for the general public to understand. **As yet, there are no studies in France that have assessed the cost of antibiotic overuse and resistance, in a global manner and written in plain, easy-to-understand language.**

Two specific studies have therefore been carried out as part of this group's work. The first, conducted by the ANSM, aimed at evaluating the economic cost of antibiotic overuse observed in France compared to a European benchmark consumption average. It is important to note that this type of analysis has never been performed in France or abroad. The second, conducted by the InVS, set out to evaluate the public health burden (mortality, morbidity) of a selection of the most common or currently emerging MDR bacterial infections in France, so as to put the aforementioned international findings into perspective.

Cost of antibiotic overuse in community medicine (ANSM study)

The ANSM study (Appendix 1) set out to put a figure on the drug expenditure incurred by excessive antibiotic consumption. Indeed, **France is ranked 5th among the European countries that consume the most antibiotics overall** according to 2012 data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net).[33] To this end, 2013 data supplied by this network of antibiotic consumption in the community sector was used. Hospital data was excluded however, as it is incomplete to date.

On the basis of European consumption data it was possible to define a benchmark consumption average, for each major class of antibiotics (level 3 of the Anatomical Therapeutic Chemical classification system, ATC). This is expressed in DDD per 1000 inhabitants per day, according to three scenarios on the basis of:

1. average consumption of antibiotics measured in the community sector across European countries
2. average consumption in the 12 most developed European countries, in reference to their GDP as indicated by Eurostat
3. average consumption in the three most "virtuous" (or best-performing) countries in terms of antibiotic consumption, out of the 12 above.

The public medicines database[34] was used to obtain the retail prices for each antibiotic, to which the dispensing fee was added, and to put a value on the amounts declared by the pharmaceutical industry to the ANSM. For each major ATC3 class, the turnover was thus recalculated and then divided by the number of DDD consumed to calculate the average price of an antibiotic DDD in France.

The costs associated with prescriptions, for example nursing procedures when an antibiotic is administered parenterally, were not taken into account.

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31 French Institute for Public Health Surveillance (InVS). Thematic report on "Résistance aux anti-infectieux". Available at http://www.invs.sante.fr/ratb

32 French National Agency for Medicines and Health Products Safety (ANSM). L'évolution des consommations d'antibiotiques en France entre 2000 et 2013. ANSM, 2014, 36 p. Available at: http://ansm.sante.fr/Dossiers/Antibiotiques/Bien-utiliser-les-antibiotiques/

33 ECDC. Surveillance of antimicrobial consumption in Europe, 2012. ECDC, 2014, report, 82 p. Available at: http://ecdc.europa.eu/en/activities/surveillance/ESAC-Net/

34 French public medicines database. Available at: http://base-donnees-publique.medicaments.gouv.fr/

For each major ATC3 class, the difference was calculated between the consumption observed in France and the one chosen as the benchmark for Europe. A value was then put on this difference for the whole of France based on the average price of a DDD. On the basis of the total of all these differences, valued per ATC3 class, the expenditure incurred in France by the overuse defined in this way could be expressed in figures.

These analyses show that the annual expenditure associated with antibiotic overuse in France in community medicine is estimated to be EUR 71, 178 or 442 million depending on scenario. This represents **0.3%, 0.7% or 1.7% of annual expenditure of reimbursed medicines in community medicine** according to the national healthcare accounts (2013).

This expenditure is strongly influenced by the choice of scenario being considered. The first corresponds to a 25% drop in antibiotic consumption, observed currently in France. The second assumes a 30% drop while the third assumes a 60% drop. This expenditure also depends to a large extent on the antibiotic consumption structure per ATC3 class. Indeed, there is a 1 to 14 ratio between the cost of a DDD for the least expensive ATC3 class (J01A, tetracycline, €0.35/DDD) and the most expensive class (J01X, other antimicrobials, €4.99/DDD). Insofar as the highest French consumption is observed in those classes whose average cost is low (beta-lactam antibiotics and penicillins), **the impact of a drop in consumption in cost terms would be limited**.

The three scenarios defined by the ANSM confirm that the high consumption of antibiotics in France incurs a direct cost for the community. Although it represents but a small fraction of annual drug expenditure, this cost cannot be overlooked, for **it is likely to be carried over to public health measures, for example promoting responsible antibiotic use.** The third scenario is the most ambitious for it involves aligning France with those European countries that consume the least antibiotics. This necessarily takes a long-term perspective and prompts questions over the optimum level of consumption to be achieved in France. **The first scenario is the most reasonable today, and therefore corresponds to the target decreases set in 2012 when the 2011-2016 national alert plan on antibiotics was published**.[35]

Cost of antibiotic resistance (InVS study)

The InVS study (Appendix 2) aimed at estimating the public health burden (morbidity, mortality) of MDR bacterial infections in France. It used similar methods to those employed by the ECDC,[36] but which were nonetheless adapted to the French context. This study took the most recent data available into account, both in terms of surveillance of MDR bacterial infections and parameters from the literature.

The MDR bacteria considered were as follows:

- methicillin-resistant *Staphylococcus aureus* (MRSA)
- vancomycin-resistant Enterococci
- third generation cephalosporin-resistant *Klebsiella pneumoniae* and *Escherichia coli*
- *Klebsiella pneumoniae*
- *Acinetobacter spp.*
- carbapenem-resistant *Pseudomonas aeruginosa.*

35 French Ministry for Health. Plan national d'alerte sur les antibiotiques 2011-2016. Available at: http://www.sante.gouv.fr/IMG/pdf/Plan_antibiotiques_2011-2016.pdf

36 ECDC and EMEA. The bacterial challenge: time to react. ECDC, 2009, report, 54 p. Available at: http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_To_React.pdf

The panel thus defined was not exactly the same as the one used by the ECDC, as it particularly excluded pneumococci with reduced susceptibility to penicillin, which are not MDR bacteria in the strict sense of the term.

On the basis of EARS-Net data,[37] it was possible to estimate the number of MDR isolates involved in invasive infections in 2012 in French laboratories belonging to this network. This estimate was adjusted for the estimated coverage of these French laboratories. It was extrapolated to other infectious sites by applying distribution ratios from the 2012 National Prevalence Survey of nosocomial infections and a targeted literature review. The number of deaths attributable to MDR bacterial infections was estimated by using the attributable mortality rates from a literature review. The methods and different parameters used were critically reviewed by a group of external experts.

The number of MDR bacterial infections occurring every year in France, according to the InVS study, is estimated to be around 158,000 (127,000 to 245,000), almost 16,000 of which are the most serious invasive infections. The corresponding incidence is estimated to be 1.83 cases (1.48 to 2.85) for 1,000 bed-days. **MRSA and 3GC-resistant enterobacteriaceae are responsible for 103,000 infections (90,000 to 172,000), i.e. 65% (70 to 75%) of all inventoried infections, with an estimated incidence of 1.38 cases (1.04 to 2.00) for 1,000 bed-days.** Lastly, **the annual number of deaths that can be directly attributed to these infections is estimated to be 12,500 (11,500 to 17,500), 2,800 of which are linked to invasive infections.** MRSA, 3GC-resistant *E.coli* and carbapenem-resistant *Psuedomonas aeruginosa* infections are responsible for 88% (90 to 92%) of these deaths.

These findings provide the first ever estimate of the burden of MDR bacterial infections in France. They confirm that the danger is significant, particularly from 3GC-resistant enterbacteriaceae and MRSA infections. Given the methods employed and the limits mentioned above, **these findings underestimate the real burden of antibiotic resistance in France.** They do, however, justify by themselves the efforts being made to tackle this issue through national plans and the special working group for keeping antibiotics effective.

37 ECDC. Antimicrobial resistance surveillance in Europe 2013. ECDC, 2014, report, 211 p. Available at: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/

Taking human health research further

Given the time set aside for the special working group for keeping antibiotics effective to conduct its work, it was not possible to perform all of the research considered relevant. **The working group has therefore listed several recommendations below for guiding future research:**

- **Build on the ANSM study by calculating, for the hospital sector, the potential savings of reduced antibiotic consumption:** the ESAC-Net hospital data is not of a high enough quality to do this, but it would be possible to achieve this through an analysis of the ATB-Raison data,[38] based on a hypothesis of a 2% decrease in antibiotic consumption per year (to return to the level of use observed four to five years ago);
- **Add a prospective section to the InVS study:** by taking an approach based on certain scenarios, it would be possible to estimate the public health burden of resistance if the rates currently observed continued to rise for want of adequate control measures;
- **Add a medico-economic section to the InVS study:** beyond the morbidity/mortality estimates already produced, the cost estimate of MDR bacterial infections in France must include the cost of their medical care (in hospitals and in the community) as well as their societal cost. Other indicators (potential years of life lost for example) must also be produced so that comparisons with other diseases may be carried out – given the sometimes striking differences in the populations affected;
- **Promote medical and economic research and its application to antibiotic resistance:** as highlighted in the working group's literature review, such studies are still few and far between, particularly in France. Evaluation of public health interventions (cost of MDR bacterial infection control or prevention) and quantification of the effects of resistance on the overall healthcare system economy should be encouraged;
- **Study the serious adverse effects of antibiotics:** exploration of pharmacovigilance data available at the ANSM would usefully round off the previous analyses by estimating their number and evaluating the cost of their treatment.

Apply the research on antimicrobial resistance to the animal health sector

The working group called on an expert from the French Agency for Food, Environmental and Occupational Health & Safety (Anses), a specialist in antibiotic resistance in the field of animal health. **The possibility was therefore considered of applying all or part of the work considered in human health to the animal health field, which is subject to a French Ministry for Agriculture dedicated "Antibiotics" plan.**[39]

That said, there are major differences between these two fields that require some key parameters to be redefined for veterinary medicine. Given the group's members and its work calendar, it was not possible to produce any figures at this stage. The considerations below are preliminary and come with recommendations for carrying out a certain number of measures in the animal health field.

First, it should be pointed out that, today, the trends observed in veterinary medicine are very different from those observed in human medicine. Indeed, the volume of veterinary antibiotic sales has been falling steadily for more than ten years, especially since the EcoAntibio plan was set up: -46.7% since 1999, -34.0% over the

38 Nosocomial infection surveillance, investigation and alert network (Raisin). Surveillance nationale de la consommation des antibiotiques dans les établissements de santé : réseau ATB-Raisin, résultats 2013. Raisin, 2015, report, 116 p. Available at: http://www.invs.sante.fr/atb-raisin

39 French Ministry for Agriculture. Plan d'action EcoAntibio 2012-2017. Available at: http://agriculture.gouv.fr/plan-ecoantibio-2017

past five years and -10.6% between 2012 and 2013.[40] **In some sectors, animal exposure to antibiotics has fallen dramatically.** For example, between 2010 and 2013, 82.5% fewer grower pigs were recorded as undergoing broad-spectrum cephalosporin treatment. At the same time, the levels of antibiotic resistance dropped sharply, particularly to critical antibiotics.[41] This shows that assessing the cost of antibiotic overuse and resistance during a period of significant reduction does not involve the same operational perspective as in human medicine, which is facing the opposite problem.

For all that, the question of the cost of resistance in veterinary medicine *is* relevant, even if it requires adjustment of the indicators. This is because **the economic factor is predominant in animal health, and the monetary cost of resistance is not borne by society at large via health insurance.** Each professional organisation bears the additional cost of treatment that may be extended, and the proportion of the antibiotic costs carried over to the price of foodstuffs is more or less unknown. The societal and ethical cost does not strike the same chord with us either since animal mortality is part of our social model. Several types of cost (cost of increased animal mortality due to MDR bacteria, cost of conventional stockbreeding versus alternative breeding, etc.) may nonetheless be measured. **They may serve to raise awareness and may therefore have a collective impact.**

Given the diversity of livestock, special attention should be paid during this work to the way in which excess animal mortality is correlated to antibiotic resistance. For the comorbidity factors normally referred to in humans are not relevant for animals. The analysis of the cost of resistance in veterinary medicine must also factor in the challenges differently, depending on whether they are shared with humans (ESBLE), to a small extent (MRSA) or not at all (*Pseudomonas aeruginosa*).

The European comparison of the health of human populations as regards their level of antibiotic use is relevant, for it is based on one and the same living species. But livestock varies significantly from one country to another, such that it makes no sense to define a single average level of use to be used as a benchmark. It would, however, be worth conducting a comparative review of the therapeutic classes used in Europe, according to a common denominator (same infection, same animal species, same production method, etc.). **Moreover, the question of imports (animals and food), probably more complex than that of human populations, merits specific analysis.**

Finally, as with humans, alignment with the work of the "Environment" working group of the special working group for keeping antibiotics effective would be vital, as the cost of resistance (human and animal) is also that of environmental pollution. **Quantitative approaches on this subject are almost unheard-of, in the same way as they are concerning the cross-linked animal-human costs of resistance.**

In conclusion, the group believes that an analysis of the cost of antibiotic overuse and resistance is also relevant in veterinary medicine. It therefore recommends **forming a multidisciplinary group in the future bringing together vets, economists, epidemiologists, sociologists, microbiologists and institutional and economic stakeholders** with a view to:

- **defining the relevant indicators to monitor for the animal health field**, based on the aforementioned different parameters;
- **conducting, with the National Veterinary Medicines Agency (ANMV), a similar study to the one carried out by the ANSM on antibiotic overuse;**
- **conducting, with the Anses and professional operators, a similar study to the one carried out by the InVS for the cost of resistance;**

40 French National Agency for Veterinary Medicine (ANMV). Suivi des ventes d'antibiotiques veterinaries, 2014. Available at: https://www.anses.fr/fr/content/suivi-des-ventes-dantibiotiques-v%C3%A9t%C3%A9rinaires
41 French Agency for Food, Environmental and Occupational Health & Safety (Anses). Bilan 2014 du réseau d'épidémiosurveillance de l'antibiorésistance des bactéries pathogens animales (Résapath). Available at: https://www.anses.fr/

- **continuing discussions on the cross-linked additional costs between humans and animals** (the respective proportion of costs carried over for each) **and the overall additional costs among humans and animals on the environment** (environmental pollution from antibiotic residues and antibiotic-resistant bacteria).

Responsible antibiotic use

The "responsible antibiotic use" working group, coordinated by Prof. Céline Pulcini (Nancy Teaching Hospital), has been tasked with **coming up with proposals for reducing antibiotic consumption and improving the quality of antibiotic prescription.** Made up of stakeholders representing the community medicine, hospital and veterinary medicine sectors, pharmaceutical industry and public agencies, the group looked at the problem of the over-prescription of anti-infectives from every angle. This "**One Health**" approach enabled the recommendations to be adapted to all types of prescriber.

Before embarking on any discussion, **different groups of healthcare professionals and experts were asked to suggest measures for improving antibiotic use.** The AC-2-BMR association, French Language Infectious Pathology Society (SPILF), Academic College for Infectious and Tropical Diseases (CMIT) and the European Study Group for Antibiotic Policies (ESGAP/ESCMID) all took part in this idea-gathering session.

Based on their ideas, the group met four times at the French Ministry for Health to identify and discuss the most interesting and feasible among them. **A Delphi-like method was set up to reach a consensus as far as possible on a small number of proposals.** The group also referred to antibiotic plans set up in Europe,[42] [43] the United States[44] and Australia[45] as well as World Health Organisation publications, to ensure that their approach had an international outlook.

Various stakeholders outside of the working group were also interviewed to get their view of the ideas selected:

- Dominique Monnet, from the European Centre for Disease Prevention and Control (ECDC),
- Luc Barret, National Medical Advisor at the French National Health Insurance Fund for Salaried Employees (CNAMTS),
- Directorate-General for Health (DGS), Directorate-General for Care Provision (DGOS) and the Directorate-General for Social Cohesion (DGCS) at the French Ministry for Social Affairs, Health and Women's Rights,
- National College for General Practitioner-Teachers,
- Observatories for Medicine, Medical Devices and Therapeutic Innovation (OméDIT) in the Centre-Loire Valley and Aquitaine and Guadeloupe regions,
- Antimicrobial stewardship medical advisors on the SPILF's Infectioflash hand-out list,
- French Federation of General-Practitioners (MG France) and Confederation of French Medical Trade Unions (CSMF).

42 Plan national d'alerte sur les antibiotiques 2011-2016: http://www.sante.gouv.fr/IMG/pdf/Plan_antibiotiques_2011-2016.pdf
43 Plan EcoAntibio: http://agriculture.gouv.fr/IMG/pdf/PlanABR-FR-2012-BD_cle8fc22e.pdf
44 National Action Plan for Combating Antibiotic-Resistant Bacteria, March 2015: http://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf
45 Australia's First National Antimicrobial Resistance Strategy 2015-2019 "Responding to the Threat of Antimicrobial Resistance", June 2015: http://www.health.gov.au/internet/main/publishing.nsf/Content/1803C433C71415CACA257C8400121B1F/$File/amr-strategy-2015-2019.pdf

Antibiotics: their use by healthcare professionals has become commonplace

Antibiotic prescription continues to be based on personal judgement

In France, prescribing antibiotics continues to be commonplace, and based on personal judgement. And yet, in the community sector, there are a few structures that offer assistance with medical decisions, particularly two **Regional Antimicrobial Stewardship Centres** (CRCA: MedQual and Antibiolor). Other local networks – most of which are not financed – also contribute to responsible antibiotic use.

In the hospital sector, the role of lead infectious disease advisors is to oversee the antimicrobial stewardship policy and to advise prescribers. **But they are either too few in number or not sufficiently trained for carrying out all of their day-to-day tasks.** On the whole there is no specific funding for this position within healthcare entities and it is usually staff already working in infectious diseases who must find extra time to carry out this role. And yet **antimicrobial stewardship programmes in hospitals are overseen by an Operational Multidisciplinary Antimicrobial Stewardship Team, much like operational hygiene teams, made up of at least three specialists: the antimicrobial stewardship advisor, a pharmacist and a microbiologist.**

These organisations have a positive impact at several levels,[46] [47] in the hospital and community sectors alike. They help to reduce antibiotic consumption, improve antibiotic prescription and patient care and to reduce bacterial resistance.

Assessment of responsible antibiotic use is incomplete

In community medicine, the Payment on the basis of public health objectives (ROSP) scheme is applied in addition to the payment-per-procedure method to encourage high-quality medical practice by attributing a value to the achievement of targets set by the convention partners and assessed on the basis of indicators. However, this scheme **only includes two indicators on antibiotic treatment for GPs**: percentage of generic medicines and antibiotic prescriptions in 16-65 year-old patients who do not suffer from a chronic condition.

In the hospital sector, the Composite index on responsible antibiotic use (ICATB2) aims at improving patient care and preventing bacterial resistance to antibiotics. Assessed as part of the certification process, this indicator reflects a healthcare entity's commitment to an antimicrobial stewardship programme. **But the score is not subject to systematic inspection of evidence.** Some 10% of entities are inspected every year by Regional Health Agencies (ARSs), and this declarative data therefore often overestimates reality.

Some 600,000 dependent elderly people live in care homes (EHPADs) in France. **Although antibiotic consumption and the prevalence of bacterial resistance are high in such places,[48] there are no regulatory obligations at present as regards an antimicrobial stewardship policy in them.** The coordinating doctor in these homes is responsible for coordinating the internal medicines policy, in liaison with the residents' prescribing doctors and with the support of the allied healthcare staff. Halfway between community and hospital care settings, this organisation results in antibiotics frequently being prescribed over the phone. In the same way, **nurses and care staff play a key role in prescribing** since they are in charge of taking patients' samples and reporting the first observations – despite the frequent lack of any specific training in antibiotic treatment.

Finally, **there are no measures in veterinary medicine aimed at "big" prescribers or consumers of antibiotics.**

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46 Interventions to improve antibiotic prescribing practices for hospital inpatients. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M. Cochrane Database Syst Rev. 2013 Apr 30;4:CD003543

47 Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. Wagner B1, Filice GA, Drekonja D, Greer N, Macdonald R, Rutks I, Butler M, Wilt TJ. Infect Control Hosp Epidemiol. 2014 Oct;35(10):1209-28. doi: 10.1086/678057. Epub 2014 Aug 21.

48 Strategies and challenges of antimicrobial stewardship in long-term care facilities. Dyar OJ, Pagani L, Pulcini C. Clin Microbiol Infect. 2015 Jan;21(1):10-9

Courses of antibiotics are still too long

There are currently no restrictive measures to limit the length of time a doctor can prescribe a course of antibiotics for, whether in the hospital sector, community sector or in elderly care homes. The ICATB2 score targets the re-evaluation of some critical antibiotics. Lastly, **the Programme for preventing hospital-acquired infections (PROPIAS)[49] recommends that any courses of antibiotics lasting longer than 7 days be re-assessed by a senior professional.**

Despite all that, **the literature documents that reducing the treatment duration to the strict necessary enables antibiotic use to be cut down on without any negative impact on patient prognosis.** What's more, this type of action limits the emergence of antimicrobial resistance.

Recommendations on antibiotic treatment are readily available, but only a few of them have been validated by the French National Authority for Health (HAS). As such, doctors do not have an official, clear reference to help them prescribe antibiotics better. There are no general recommendations in France on treatment durations either. **The SPILF recommendations group is planning to provide healthcare professionals with recommendations on shortening treatment durations from the autumn of 2015.**

Healthcare professionals have a role to play in educating patients in responsible antibiotic use.

Little is being done at present to promote prescribers' commitment to prescribing antibiotics responsibly, even though the use of some tools such as a public commitment charter have helped to reduce antibiotic use.[50] **A commitment charter from the Hospital Federation of France (FHF), drawn up in partnership with the SPILF and Le Lien patients' association, is currently in use in all public hospitals**.[51] This is one of the PROPIAS' measures: it provides patients with more information about the importance of responsible antibiotic use, may help healthcare professionals to communicate more clearly on the subject, and gets prescribers publicly involved in prescribing antibiotics better.

Furthermore, training in responsible antibiotic use for healthcare professionals in human and animal medicine alike – whether or not they prescribe antibiotics – is a key measure promoted by both WHO and the PROPIAS. Indeed, several studies indicate gaps in the initial and ongoing training of healthcare professionals in France.

Lastly, antibiotic use can be reduced if communication is improved between doctors and their patients. And yet, **prescribers do not have appropriate resources for cases in which no prescription is given, or for giving information.** This means that, in France, 9 out of 10 appointments result in a prescription for medicine being given. Providing healthcare professionals with appropriate aids for explaining antimicrobial resistance can help patients to take their antibiotics responsibly, and to limit self-medication as well as environmental pollution by unused antibiotics.

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49 Programme national d'actions de prévention des infections associées aux soins: http://sante.gouv.fr/programme-national-d-actions-de-prevention-des-infections-associes-aux-soins-propias.html

50 Nudging guideline-concordant antibiotic prescribing: a randomized clinical trial. Meeker D, Knight TK, Friedberg MW, Linder JA, Goldstein NJ, Fox CR, Rothfeld A, Diaz G, Doctor JN. JAMA Intern Med. 2014 Mar;174(3):425-31

51 http://www.infectiologie.com/site/_actualite_detail.php?id_actualite=469

Step up the antimicrobial stewardship policy across the medical practice board

Provide specific, sustainable funding for Regional Antimicrobial Stewardship Centres (CRCAs) and Multidisciplinary Antimicrobial Stewardship (MAS) Teams

- Regional Antimicrobial Stewardship Centres (CRCAs)

As part of the current territorial reform, a CRCA is to be opened in each region in Mainland France, along with similar structures in French Overseas *Départements* and Regions – Overseas Communities (DROM-COM). The plan is for these centres to make use of existing structures[52] so as to offer advice, carry out surveillance and administer training on responsible antibiotic use. As central stakeholders in the local antimicrobial resistance prevention strategy, they are due to oversee a network of lead advisors at regional level, who are likely to take part in the region's antimicrobial stewardship programme in the hospital sector, community sector and elderly care homes. Another role would be to take stock of existing resources at regional level and to provide financial or logistical support for projects that the steering committee consider worthwhile. **The setup and running of one CRCA in each region represents a total cost of EUR 5 million per year (Appendix 3).**

The CRCA must be managed by a professional with clinical and research experience and the necessary skills for coordinating the antimicrobial stewardship programme. Since the CRCA will be tasked with overseeing local research, communicating on the antimicrobial stewardship policy and conducting regional prospective research, **professionals working in the community sector must be involved in running and coordinating such measures.** The CRCA would be **coordinated by a national committee made up of CRCA chairs and coordinators** whose role it would be to pool experiences and the tools developed locally (e.g. Antibioclic and the Côté Pragmatique antibiotic prescription hotline for GPs in the Parisian region).

- The lead infectious diseases advisor and Multidisciplinary Antimicrobial Stewardship Teams

In hospitals, the current definition of the role and responsibilities of the lead infectious diseases advisor and the Multidisciplinary Antimicrobial Stewardship (MAS) Team makes no mention of the time that should be set aside for each task (Appendix 4). And yet these professionals must juggle management of the antimicrobial stewardship programme with patients' appointments in order to guide and advise prescribers.

The lead infectious diseases advisor and MAS Team must forge a relationship based on trust with the entity's prescribers to facilitate the setup of antimicrobial stewardship measures (some of which can be restrictive, such as review of critical antibiotics). Under such conditions, **the lead infectious diseases advisor must be a medical clinician** for s/he must be able to go and examine patients alongside the prescribers when necessary, in order to provide educational support and monitor responsible antibiotic use in certain predefined situations. **The lead advisor's role is not to make decisions in clinicians' place each time an antibiotic is prescribed; rather, to provide them with guidance and training.**

Lastly, the lead advisor must be "qualified for the job".[53] **This means a Specialised Degree (DES) in Infectious and Tropical Diseases needs to be created**. The number of jobs available in this speciality may be indexed on the number of lead advisors needed for example (infectious disease specialists do not act solely as lead advisors in this area).

This measure calls for 2,000 Full-Time Equivalents (FTE) within the MAS Team (including 1,100 for lead advisors), amounting to a total cost of EUR 200 million per year. A 20% reduction in overall antibiotic use would free up enough funding to finance this proposal, all the while improving responsible antibiotic use

52 Antimicrobial Stewardship advisor for the French Regional Health Agency (ARS), regional vigilance and support structures, CClin, Arlin, Omédit

53 ICATB2 ATBM4a criterion: tick yes if the lead advisor has an Additional Specialised Degree (DESC) in Infectious and Tropical Diseases, or a University Degree (DU) in antibiotic treatments or a qualification in infectious diseases

overall, for these professionals would become key stakeholders in the local antimicrobial resistance prevention strategy.

Promote responsible antibiotic use across all practices

In the community sector, it is necessary to promote responsible antibiotic use, provide prescribers with guidance and be able to take action among "big" prescribers. **As part of the forthcoming negotiations on medical convention in 2016, more indicators on antibiotic treatments must be added to the ROSP to increase the appeal of using this class of medicines responsibly.** Such indicators will have to be easy to establish, understand and assess, and statistically robust. Examples can already be found in the literature as well as ongoing research within France and Europe,[54] such as the indicator on amoxicillin-clavulanic acid, fluoroquinolones and 3GC prescriptions as well as the seasonal variation in overall antibiotic prescriptions. **These indicators on antibiotic treatments should be extended to other specialities where antibiotics are heavily prescribed** (for example in paediatrics and ENT).

In technical terms it is currently difficult for healthcare professionals to compare their practices with those of their peers. With this in mind, **the CNAMTS must be given sufficient means for being able to send to all primary care prescribers an annual detailed profile of their antibiotic prescriptions, showing a comparison with the *département* level.** This may contain the ROSP indicators, indicators validated by the literature or the Rapid diagnostic test order level, again showing a regional comparison. This profile should ideally include clinical indicators, cross-linking diagnostic and prescription data, from datasets and Prescription Aiding Software, and on the basis of indicators validated by the literature. What's more, the CNAMTS will soon have regional data available on bacterial resistance through the MedQual-Ville tool, and this data could be added to the annual profile for information.

Finally, **the CNAMTS must have the necessary resources for monitoring all of these antibiotic prescription profiles so that it can then target "big" prescribers** whose prescription level in relation to their patient type is a long way above the national average. The Health Insurance System would thus continue to support all prescribers through peer visits, and may undertake a targeted action plan where "big" prescribers are concerned. Health Insurance Delegates may take CNAMTS memo sheets, ROSP indicators and the prescriber's profile along with them when they visit healthcare professionals. **If, despite a warning from these Delegates, a prescriber were to continue to blatantly overprescribe, the CNAMTS would undertake a series of steps to try and improve the prescriber's practices** through compulsory training and regular assessment (reading back over medical records, checking patients' records against the indicators, on-site inspection and interview with the prescriber, supervision during medical practice). Legal proceedings may have to be taken should deviant and dangerous practice continue.

In the hospital sector, the ICATB is biased because of the declarative nature of this indicator. To limit overestimation, healthcare entities should systematically send supporting documents to prove the ICATB2 to Regional Health Agencies. Likewise, **some indicators may become compulsory**, such as the number of FTE dedicated to the lead advisor(s) or the level of qualification of prescribers. Accordingly the overall ICATB score would be 0 if these compulsory indicators were not met. With the hospital V2014 certification procedure underway, **antimicrobial resistance prevention must be included in the Priority Required Practices (PEPs)[55] in the next certification guide**,[56] which is currently being revised and needs to be made shorter. Lastly, **a new ICATB2 is needed and must include new indicators** (surgical antibiotic prophylaxis, proportion of doctors trained, specific training of lead advisors, FTE/number of beds ratio for lead advisors, process indicators assessing the activity of lead advisors, etc.). It will therefore be necessary to amend the decree on the ICATB.

54 European project http://drive-ab.eu
55 These are criteria for which particularly important expectations are expressed
56 HAS: http://www.has-sante.fr/portail/jcms/r_1495044/fr/la-v2014

Moreover, to be able to assess practices more effectively, **the working group recommends that a compulsory section on "Antibiotic treatment assessment" be added to all five-year national surveys on the prevalence of hospital-acquired infections** (conducted in healthcare entities).

An antimicrobial stewardship programme needs to be set up in elderly care homes. With the help of the CRCA, the medical coordinator must have the necessary means for setting up an antimicrobial stewardship programme in the entity. **This must form part of his/her responsibilities.** It may involve providing prescribers working in the elderly care home with recommendations, or training staff.

In the same way, an ICATB certification score tailored to elderly care homes is required. This must be simple to establish so that all entities are happy to accept it. As such, the ARS certification file may contain the doctors' and carers' qualification levels, the recommendations made available to the entity's staff, antibiotic plan documentation in the resident's medical file, the number of prescriptions and cytobacteriological examinations of urine. That said, consideration should be given to the necessary legal support for establishing such indicators, so as to distinguish elderly care homes with their own pharmacy from those without. For the former, they could have a similar certification process to the one conducted for healthcare entities. For the latter, Regional Health Agencies would need to be called on for the three-yearly or five-yearly certification.

In veterinary medicine, if the prescription level far outstrips the national targets (set per prescribing vet on the basis of his or her patients), the prescribing vet and/or stockbreeder must set up a detailed action plan. Detailed antibiotic prescription data must already be available for this measure to take place, and national targets need defining.

Providing prescribers with antibiotic treatment recommendations

If practices are to be improved, and assessed in a consistent manner, doctors must be provided with national recommendations that are updated at regular intervals on antibiotic treatment procedures in the most common clinical situations. Approved by the French National Authority for Health (HAS), these must be incorporated as digital decision aids in the datasets of the healthcare information systems and prescription-aiding software.

Courses of antibiotics should be prescribed for the shortest time possible, as the HAS recalls in its memo entitled *"Principes généraux et conseils de prescription des antibiotiques en premier recours"*[57]. **The working group recommends indicating a single prescription duration and getting rid of the maximum limit in prescription ranges**. This means that the recommendations would no longer present a treatment duration of between 7 and 10 days, but of 7 days only.

Reducing treatment durations

In the community sector, the initial prescription for a course of antibiotics should be limited to 7 days at the most. Most infections encountered outside of the hospital environment do not require more than a week of antibiotics. What's more, in the event that an illness justifies more than 7 days' treatment (such as complicated urinary tract infections involving the parenchyma), in most cases the patient should be re-examined. **This means that healthcare information systems available in the community sector must factor in systematic review of antibiotic treatments > 7 days.**

In this way, patients would have to take two prescriptions (initial and repeat prescription for antibiotics with no fixed duration) to the pharmacy to justify treatment lasting more than 7 days. If the initial prescription were to exceed 7 days, the pharmacist would not be authorised to issue more than 7 days' treatment. **This measure must be phased in over time, with an educational reminder for two years, and then become a definitive requirement, whereby initial prescriptions for a course of antibiotics to be issued for more than 7 days must be refused.**

57 General principles and advice for prescribing antibiotics as first-line treatments

In hospitals, courses of antibiotics lasting more than 7 days must be systematically reviewed by the lead advisor (provided that there is specific funding for lead advisor positions, see above). The difficulty in planning an automatic review of courses of antibiotics at D3 and D7 calls for **specifications and a certification to be established at national level for digital prescription software in healthcare entities.**

In the community and hospital sectors alike, these healthcare information and prescription systems would also contain a summary function, called the patient's "antibiotic record" (much like the "transfusion record") for enabling better follow-up of prescriptions. This antibiotic record must also be put in the patient's personal medical record when it is in use.

Setup of this measure on treatment durations depends on national recommendations validated by the HAS on treatment durations being available (see above).

Providing healthcare professionals with communication aids

All prescribers (in the community, hospital, elderly care home and veterinary sectors) must demonstrate their commitment to responsible antibiotic prescription. **For that, a public commitment charter must be made available to them so that they can choose freely to become involved in antimicrobial stewardship.** This will remind prescribers of the need to use the rapid diagnostic tests that the CNAMTS has placed at their disposal, particularly in general practice, paediatrics and A&E. The charter will be signed by the prescriber and put on display in the waiting room.

University lecturers will be asked to sign a specific commitment charter, focusing on antimicrobial stewardship and the use of rapid diagnostic tests among house officers. This must be attached to applications, along with the annual detailed profile of antibiotic prescription published by the CNAMTS. The department of general practice will be entitled not to recruit lecturers whose antibiotic treatment practices do not seem to conform to best practice.

Furthermore, university courses need updating so that core initial training on responsible antibiotic use and resistance becomes compulsory for all healthcare professionals, including house physicians, dentists, midwives and pharmacists. Likewise, continuing education for all professionals (doctors, dentists, midwives, pharmacists, State-qualified nurses and prescribing vets) on antibiotic treatments, responsible antibiotic use and bacterial resistance must become compulsory, at intervals to be defined.

The antibiotic prescribing practices of prescribing healthcare professionals (with the exception of vets) will be assessed on a regular basis, at intervals to be defined. Peer groups are a priority strategy for training and assessing practices in the community sector. In multidisciplinary healthcare centres, subscribing to the review of antibiotic treatments as one of the priorities in the specifications must encourage collective responsible use of antibiotics.

Lastly, prescribers must have appropriate information and communication tools for patients they suspect of having an infection. An **"information pack"** will be supplied to them, which will involve handing patients different information documents depending on their situation.

- In this way, **where an infection does not require an antibiotic**, the doctor will give the patient a **"non-prescription form". This will be presented in the form of a prescription booklet – or publishable on a healthcare information system – and explain why the healthcare professional has not prescribed antibiotics.** This guidance will help to ease the pressure that patients can place on doctors – who still gives them a "prescription" for all that – and helps to increase patient accountability. This document is currently being finalised by the Directorate-General for Health and CNAMTS, and should be available from autumn 2015.
- **When an infection requires an antibiotic prescription**, the doctor will publish a "**specific prescription form**". **Automatically programmed in the healthcare information system so as not to increase the healthcare professional's workload, this specific prescription form** will contain educational messages on

responsible antibiotic use and bacterial resistance, particularly regarding completing the course of antibiotics exactly as prescribed and recycling unused antibiotics according to the guidelines. **Incorporated in the specifications of the certification of healthcare information systems, all the healthcare professional will have to do is confirm and print the specific prescription.** What's more, the CNAMTS will supply doctors with specific prescription booklets along with more detailed information sheets on antimicrobial resistance to help round off the prescription should their patients ask for more information.

Other responsible use and communication tools are necessary. Use of rapid diagnostic tests whose merits have been demonstrated in the literature must be encouraged via regulations. **In this regard, an appropriate budget and circuit would need to go towards financing the use of such tests.** Moreover, as part of a national information campaign, **the CNAMTS will have to once again raise the awareness of childcare professionals as well as nurseries and parents at regular intervals and over the long-term, by handing out "The practical guide to infectious diseases" and other information documents on responsible antibiotic use and bacterial resistance.**

Support initiatives under consideration

The working group supports the following initiatives under consideration within the different government departments:

Targeted antibiogram

As part of the national antibiotics alert plan, a Directorate-General for Health working group is developing a targeted antibiogram. This involves acting on the list of antibiotics making up the antibiogram provided to the medical clinician, by only presenting the most suitable antibiotic treatments with the least bacterial resistance. This initiative raises ethical and practical difficulties in terms of setup however (lack of human and IT resources).

The opinion of the lead advisor for critical antibiotics

For any "critical" antibiotic on the list published by the ANSM (currently being revised), the lead infectious diseases advisor must give an opinion prior to prescription. There are practical difficulties in terms of setup regarding this initiative, particularly due to a lack of human and IT resources. The measure aimed at financing lead infectious diseases advisors and MAS teams is essential for getting this initiative up and running.

Definition of the initiative:

For last-resort antibiotics, the following is advocated:

- an initial prescription limited to 3 days, also mentioning the clinical data enabling the pharmacist to dispense the antibiotics in a controlled manner;
- a new prescription is necessary after D3;
- the lead advisor's opinion must be sought before D3 and again on D7;
- controlled dispensing by the pharmacist;
- closer monitoring in terms of consumption and resistance.

For antibiotics where resistance is particularly high, the following is advocated :

- an initial prescription limited to 3 days;
- a new prescription is necessary after D3;
- controlled dispensing by the pharmacist;
- closer monitoring in terms of consumption and resistance

Dispensing antibiotics dose by dose: trial

A trial involving the dispensing of antibiotics dose by dose is underway in 100 dispensing pharmacies across four French regions (Ile-de-France, Limousin, Lorraine and Provence-Alpes-Côte d'Azur). The first official findings from this project are due to be published in the coming months.

Communication, information and education

Coordinated by Claude Rambaud (Ciss), the "communication, information and education" working group was tasked with **coming up with recommendations for the next communication and information campaign on antimicrobial resistance.** Bringing together representatives of associations, academia, the medical profession, industry and institutions, the group set out to establish the necessary conditions for a complete paradigm shift.

To formulate its proposals, the working group looked at initiatives both past and present, at national and international level (UK, the Netherlands). To this end, they interviewed :

- the CNAMTS for a rundown of the various campaigns organised over the past 10 years
- the French National Institute for Health Education and Prevention (INPES) about its information actions
- Dr Pia Touboul, from Nice Teaching Hospital, who coordinates the e-Bug training programme for France

Discussions were initiated on the philosophical, ethical and methodological approach to take for the next campaign. Below is a summary of the discussions that were held during the working group's five meetings. **These proposals involve efforts over time, with short-term (information), medium-term (communication) and long-term (education) measures. They form the core action that must be taken to sustainably raise antimicrobial resistance awareness across our society.**

We will fear infection again if our relationship with antibiotics does not change

Several communication campaigns have been organised over the last 15 years. Coordinated by the CNAMTS, they have been aimed at several audiences, taking different philosophical and methodological approaches, and their outcomes have been mixed. The working group sought to understand how these different campaigns worked, their impacts and the lessons to be learned.

« Les antibiotiques, c'est pas automatique » (Antibiotic? It's not automatic!)

From 2002 to 2005, the CNAMTS organised a sweeping campaign based on the famous slogan: "les antibiotiques, c'est pas automatique" (antibiotic? It's not automatic!). With a budget of seven million euros, the campaign was carried out through the purchase of adverts (on the television and radio, as well as posters in public places) and through visits that French Health Insurance Delegates paid to doctors. **The campaign aimed at prompting users to develop an instinctive reflex to question the need for prescribing antibiotics,** by targeting two groups: the "general public" and "doctors". **It did not set out to teach patients to understand the risk of antimicrobial resistance; rather, to offer a new form of communication on a new theme, in a light-hearted tone.**

This campaign was a hit: seeing antibiotic use fall by 24% between 2002 and 2005, i.e. the equivalent of 17.2 million courses of antibiotics were avoided. It has had a lasting impression on public minds, both in France and abroad, that can still be felt today. The effect has been even greater in children, for treating sore throats, colds and flu. **It has not resulted in a reduction in antibiotic use for bronchitis, ear infections or sinusitis though.**

« Viral, pas d'antibiotique » (Virus? No antibiotics!)

From 2005 to 2008, the CNAMTS ran a different campaign with the aim of reducing antibiotic misuse, by explaining the inefficacy of antibiotics against viruses. No particular communication was carried out on bacterial resistance. **Media coverage of this campaign was limited, and antibiotic use did not decrease.**

« Les antibiotiques, utilisés à tort, ils deviendront moins forts » (Antibiotics used wrongly don't act as strongly)

After a year with no particular communication on antibiotics, the CNAMTS organised a new campaign in 2009. Geared more towards explaining the phenomenon of resistance, this campaign was designed for "patients" and "doctors". **The campaign slogan and messages may have had limited media coverage, but they did give healthcare system users greater insight into the different illnesses (sore throat, colds and bronchitis).**

The campaign played a part in a fleeting dip in antibiotic use, for an ANSM report in July 2014 indicates that, between 2009 and 2011, antibiotic consumption in the community sector went from 29.6 to 28.2 and back to 28.7 in DDD for 1,000 inhabitants per day. Over this period, the CNAMTS concentrated most of its investment on the media.

But the campaign did not have the quantitative outcome hoped for, despite a ten-million-euro budget. Indeed, since 2012, when media investment has fallen and been concentrated online with no link with the traditional media, antibiotic use has been picking up again (29.7 in 2012 and 30.1 in 2013). **This phenomenon is continuing today, which confirms that, when no large-scale communication is taking place, consumption increases.**

« Tous ensemble, sauvons les antibiotiques » (Together, let's save antibiotics)

These ten years of communication have enabled significant savings to be made. The different campaigns have been organised with input from several partners, associations and representatives of civil society, so as to reach out to people from diverse walks of life such as childminders, nurseries, children and teenagers at school, as well as healthcare professionals. **Thanks to such action, more than 40 million prescriptions were avoided between 2002 and 2012. Accordingly, for every euro invested in each campaign, 14 euros was saved by the French Health Insurance System, in relation to the expenditure trend.** And yet, although these three campaigns have steadily brought the problem of antimicrobial resistance into the public spotlight, **the French population is still very much in the dark about it.**

The most recent campaign, aimed at informing about the risk of antimicrobial resistance, did not succeed in raising French people's awareness as it did not account for the diversity of people living in our society today. As such, a wide range of different groups of people from all walks of life, who are all interconnected, make up the "general public", but their receptiveness to public health messages varies enormously. This means that **only a few small isolated groups, having to cope with serious infectious events directly, have grasped the danger of antibiotic overuse.**

In order to raise awareness among more groups of people, the working group advocates a series of measures tailored to the different sections of civil society. A paradigm shift is necessary, but can only be achieved by forming groups of people who know the score about the risk of antimicrobial resistance. These proposals are therefore aimed at making individuals accountable in terms of their relationship with bacteria and with antibiotics, **so that the collective conscience wakes up to the need to keep antibiotics effective.** This approach is inspired by the "Antibiotic Guardian" campaign currently underway in the UK.[58] This sets out to make every citizen a "guardian" of effective antibiotics. Although it is not possible to reproduce the British campaign as is in France, **the next campaign should nevertheless highlight the danger of the resistance phenomenon and show that a long-term alternative is possible – but only if each and every one of us gets involved.**

58 https://antibioticguardian.com

Organise a far-reaching information, communication and education campaign

The next campaign will comprise several stages :

Set up a structure for overseeing the campaign

The measures advocated by the working group are all part of one major, comprehensive information, communication and education campaign. This must bring together the different identified sections of French society around a single slogan that binds them, **recalling that keeping antibiotics effective requires joint action on all our behalfs.** The working group has suggested the slogan: "**Tous ensemble, sauvons les antibiotiques**" (Together, let's save antibiotics), but this is open to change. **The measures must be taken at several intervals in order to keep the subject of antimicrobial resistance fresh on people's minds.**

A steering committee will have to be set up to validate the launch, coordination and monitoring of the actions taken for this campaign. It will encourage and showcase the cross-disciplinary work to bring down the barriers between the various stakeholders likely to carry out the different proposals. It may pool available resources to communicate on antimicrobial resistance. Lastly, it will help to draw up the specifications of the information campaign that will round off its adopted communication strategy. **It will be chaired by the Interministerial Delegate for antimicrobial resistance and report its action to the Interministerial Committee.**

This committee will be made up of the French Ministries in charge of Health, Agriculture, National Education, Research and Higher Education, the CNAMTS, the INPES, the different agencies active in the field of human, animal and environmental health, representatives of medical and allied health professional organisations, patients' associations and health industries.Ce COPIL se composera des Ministères en charge de la santé, de l'agriculture, de l'éducation nationale, de la recherche et de l'enseignement supérieur, de la CNAMTS, de l'INPES, des différentes agences intervenant dans le champ de la santé humaine, animale et environnementale, de représentants des organisations professionnelles médicales et paramédicales, et des associations de patients, et d'industries de la santé.

Centralising all knowledge on antimicrobial resistance to make information more accessible for the different sections of society

If an Internet user types "antibiorésistance" (the French word for antimicrobial resistance) into the Google search engine, more than 600,000 results are brought up. While the institutional websites make up the first search pages, **there is no one-stop portal in which all of the information available on bacterial resistance can be centralised.**

The working group therefore recommends getting a one-stop website quickly up and running that would be hosted by the French Ministry for Health and managed by the Interministerial Delegate in charge of Antimicrobial Resistance. The various institutions in charge of managing antimicrobial resistance would upload information on this website, after validation by the steering committee and its chair. **This collegiate approval stage must prevent compartmentalisation, instead helping to ensure that the information available on this platform is cross-cutting.**

Significant human and financial resources will be necessary to set up such a platform, particularly to upload information on the different websites. But **an online health information reform is underway that should lead to a single institutional platform being created. The group therefore suggests incorporating the following information into the draft reform for the website section devoted to antimicrobial resistance.**

Its role would be to inform all stakeholders. The address of this portal may be indicated on all the resources planned within the campaign (information documents, prescription documents, charter, etc.). **This tool may also help to recognise the field of infectious diseases as a medical speciality in France –** as it is in many other European countries – and to improve knowledge of this speciality among the general public and healthcare professionals.

There will be different access spaces to this portal depending on the section of society concerned, but it will still be possible to switch between these different spaces thanks to cross-cutting subjects :

- Healthcare system users :

The CNAMTS already has a website dedicated to antimicrobial resistance[59] for healthcare system users. **By advocating a complete overhaul of this website and its hosting by the French Ministry for Health, the group intends to pool skills and resources,[60] while continuing to leave oversight of this space to the CNAMTS.**

The contents of this website may be organised per section of society (children, teenagers, adults, senior citizens) or topic (responsible use, recycling, diet, etc.). **It will present scientific findings in plain, easy-to-understand language through clear definitions, simple animations, key figures and operational documents, such as the guides published by the CNAMTS[61] or the INPES. It will also present the different antimicrobial stewardship tools made available to healthcare system users** (doctors' commitment charters, use of rapid diagnostic tests and so on).

The various pages of this website will have to educate Internet users by providing specific examples. **The group is in favour of creating fact sheets on cases of antimicrobial resistance based on accounts from patients, their family and medical teams.** The point is to shed public light on actual examples of victims of antimicrobial resistance, so that different sections of society can get a real idea of the risk. **These documents may be presented in the form of interviews or reports, and made available to stakeholders who are likely to use such examples in other types of media** (web-media, television series, cinema). **There may also be a section on this website in which we imagine a world without antibiotics.**

- Professionals working in human health :

The Directorate-General for Health coordinates a website on the "2011-2016 antibiotic plan".[62] **This is designed for professionals working in human health and lists all of the publications by institutional partners. It is not very accessible to the general public, and does not give local stakeholders (government departments, healthcare staff) the opportunity to speak out.** As such, it does not feature any pages for promoting feedback gathered by the Regional Health Agencies (ARS) or presenting key indicators from different reports.

The website therefore needs to be updated so that the information it presents can be accessed more quickly by healthcare professionals and can provide guidance in responsible antibiotic use. A presentation should be given of the various tools available to prescribers, issuers and users (nurses), as well as structures (hospitals, elderly care homes, healthcare centres) :

- Prescription and decision aiding software
- Prescription documents: specific prescription form, non-prescription form
- Distance-learning programmes for professionals
- Institutional responsible use guides: recommendations, publications, etc.

This web space must also be accessible to healthcare system users, who can thus find out about good professional practices.

- Professionals working in animal health :

Setup of a website for professionals working in animal health is part of the 2012-2017 EcoAntibio plan coordinated by the French Ministry for Agriculture. A trial is due to carried out in four French regions in 2016-2017. This will be run by the veterinary profession and comprise a documentary base along with thematic factsheets.

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59 http://www.ameli.sante.fr/protegeons-les-antibiotiques/les-antibiotiques-sont-souvent-utilises-a-tort.html
60 http://www.sante.gouv.fr/antibiotiques,13573.html
61 http://www.ameli.sante.fr/fileadmin/mediatheque/pdf/Guide_pratique_maladies_infectieuses.pdf
62 http://www.plan-antibiotiques.sante.gouv.fr/

The working group supports the efforts made by the Directorate-General for Food and proposes that it be entrusted with running the space given over to animal health. Given that the agricultural industry is organised into sectors and specialities, this Directorate-General may select which institutional websites it considers the most relevant.

- Antimicrobial resistance in the environment :

Most sections of society have little understanding of the discharge of antibiotics or products selecting resistances in the environment, and it is therefore necessary to present Internet users with the ins and outs of the presence of resistance in the environment **to be able to correct widespread practices (self-medication, non-recycling of medicinal products, overuse in human and animal health)**. This web space therefore aims at explaining "natural" resistance in the environment and "acquired" resistance, linked to antibiotic and biocide misuse, as well as pollution which plays a part in resistance selection.

The working group recommends that this website be overseen by the French Ministry for Ecology, Sustainable Development and Energy, which is contributing to the discussions of the "Antibiotics and environment" group.

- Research on antimicrobial resistance :

Research on antimicrobial resistance is not coordinated at present in France. Because there is nowhere that lists current research or the teams conducting research on antimicrobial resistance, we do not have a clear idea of research in this field. In the continuity of the group on research, innovation and new medico-economic models, the common portal will have to host a space devoted to research projects.

The team set up by the French National Alliance for Health and Life Sciences (Aviesan) and French National Alliance for Environmental Research (AllEnvi) will coordinate this website. It will list the structures and research teams working on the subject of bacterial resistance, in human, animal and environmental health. It will summarise the research underway within France as well as calls for proposals. It will promote scientific articles produced by French and foreign research teams and may also help to recruit researchers by displaying job vacancies across the different research units.

Bring about a paradigm shift through a campaign that makes each and every stakeholder more accountable in keeping antibiotics effective

Tasking the CNAMTS with organising an information campaign based on traditional communication tools

The working group recommends tasking the CNAMTS – in partnership with the INPES and the steering committee – with organising a new campaign that presents antimicrobial resistance as a proven threat to the whole of society. In contrast to this bleak prospect, the campaign will have to instil the image of a better world thanks to responsible, sustainable antibiotic use.

The data presented previously in this report will have to be passed on via different types of media so as to raise awareness across society of the short and long-term risk for the healthcare system. By explaining the determining factors of antimicrobial resistance, its consequences and solutions for fighting this phenomenon, **this campaign will prompt different sections of society to question whether there is a real need for antibiotic use and to look at the actual indications of such medicines.**

The CNAMTS' role will be to mobilise the traditional information and communication channels in order to present all of the initiatives advocated in this report to the different sections of society :

- **"Tous ensemble, sauvons les antibiotiques"** (Together, let's save antibiotics): the campaign will communicate on antimicrobial resistance key figures and information so as to explain the consequences thereof, through actual examples today or from the days before antibiotics were marketed
- **"Docteur, dans mon cas, est-ce bien nécessaire de prendre des antibiotiques?"** (Doctor, in my case, is it really necessary to take antibiotics?): the campaign will also communicate on the doctor-patient relationship, particularly regarding the use of rapid diagnostic tests, abiding by the antimicrobial stewardship charter, new prescription documents, and responsible use following the guidelines.

This new campaign is to be carried out over the long-term, and may only get off the ground once information has been centralised and the different stakeholders have liaised. Indeed, **the CNAMTS will not have the resources it needs to organise a new campaign until 2016.** As a result, until a budget given over to antimicrobial resistance has been declared, the steering committee will draw up the specifications for the next campaign in the meantime.

It will have to determine a series of measures that have been tried and tested during previous campaigns and which the CNAMTS will have to put into practice. For this, the CNAMTS will make use of traditional communication tools to inform society as a whole about the risk of bacterial resistance: radio and TV adverts, purchasing of media spaces, message displays in different formats (online, on flyers), a range of fun activities for different users and online information programmes, until the national campaign is up and running.

A national event will have to be organised for the ECDC's European Antibiotic Awareness Day on 18 November 2016 to launch this campaign.

Encourage citizens to take individual action to help keep antibiotics effective

The gravity of the situation must spur each and every one of us to become accountable for the collective good that are antibiotics. The next campaign must therefore focus on civic involvement to save antibiotics.

This means that, while the CNAMTS campaign will take a "top-down" approach (from a single stakeholder to society as a whole), **the steering committee will have to put into practice the working group's various ideas for bringing about action from the "bottom-up", and get all sorts of stakeholders involved :**

- **Exhibition/museum on antimicrobial resistance**: on 30 September 2014 the Micropia museum[63] was officially opened in Amsterdam, the Netherlands. This cultural centre dedicated to bacteria helps to raise awareness among different groups of people about the need to live in harmony with microbial flora. **This concept could be imported to France, by organising exhibitions in national museums** such as the Cité des Sciences in Paris.
- National antimicrobial resistance competition: this idea is aimed at showcasing public initiatives that help to tackle antimicrobial resistance. This form of communication must encourage individuals to get personally involved for the common good. Several rewards – financial and material alike – may be awarded depending on the type of stakeholder, action or group of people educated.
- **New name for multi-drug resistant bacteria**: the working group has studied the possibility of coming up with a new French word to designate multi-drug resistant bacteria so that they are more easily identifiable in the public sphere – much like the English word "superbug". The working group was unable to come to any agreement through lack of time, but this idea could be considered during the next campaign. **The point is to find a word that hits home about the nature and risk of antimicrobial resistance**. A call for proposals could be launched through the National antimicrobial resistance competition.

All of these tools may be presented on European Antibiotic Awareness Day on 18 November 2015, when the public authorities could officially declare the need to keep antibiotics effective a "**Major national cause**", pending the launch of the CNAMTS campaign.

In connection with this campaign, the French Ministry for Health is considering including a prevention message on packs of antibiotics about responsible antibiotic use. This proposal will be presented to the pharmaceutical committee in the autumn of 2015 for discussion and validation, before being passed on to the European Medicines Agency (EMA) – the only European body able to enforce this measure within Member States.

63 http://www.micropia.nl/en/

Provide education in antimicrobial resistance at all ages, using tools that can reach out to all sections of society

- E-bug

France is a partner in the European e-bug programme. Coordinated in the UK, this educational project is being carried out across the EU Member States. **It comprises a set of digital and documentary teaching aids on the topic of infectious diseases.** A major chunk of the programme focuses on bacteria and antimicrobial resistance.

In France, information in paper format is sent to primary and secondary schools, and just recently sixth-form colleges as well, by the INPES. A website is also available to teachers and students. **These can be used as teaching aids for health education programmes, as well as Earth and Life Science classes.**

The programme is of a high standard, but it continues to be underused because of a lack of resources for developing it and due to the limited time allocated to infectious diseases in school curricula. The working group therefore advocates developing the e-bug programme into a key educational resource that can be used **in primary schools, right the way through to continuing education for healthcare professionals.**

First and foremost, secure, long-term funding must be assigned to the e-bug programme. Dr Pia Touboul, who coordinates the programme in France, estimates **this annual funding need to be EUR 40,000 at present. EUR 16,000 are needed in addition to these operating costs to develop each topic in a sector.** In total, the e-bug programme calls for significant investment (Appendix 5), but this is **necessary if general understanding of antimicrobial resistance is to improve, starting with our youngest members of society.**

The development of this resource must go hand in hand with the topic of antimicrobial resistance being put on school and university curricula, for the medical, allied health and agricultural professions. This measure aims not only at perpetuating the e-bug programme over the long term, but also at developing content with the help of teachers, academics and pupils/students themselves. Indeed, **the working group supports the initiatives currently being trialled in France to educate medical/pharmacy students in the e-bug programme, so that they can then help to teach schoolchildren on the subject.**

In the medium term, the e-bug resource may form a module of the core syllabus that all students of life sciences (medicine, nursing, pharmacy, etc.) must take, and who therefore would need to be awarded the corresponding university credits to pass their degree. **At the same time, the e-bug programme may also be used as part of the continuing education of healthcare professionals, by becoming an official module of the continuing professional development scheme (DPC) for the medical profession, once its contents have been adapted accordingly.** In this way, **the e-bug resource will provide guidance to healthcare professionals over the long term and play a continuous part in improving knowledge and practice.**

- Cross-disciplinary university projects (communities of universities and institutions/COMUE)

Antimicrobial resistance must not be a subject solely for study on healthcare courses. Cross-disciplinary courses can be developed on the basis of this topic which bring together a wide range of stakeholders well beyond the university realm.

The working group would like to encourage the creation of cross-disciplinary projects that involve researchers, professors, students and professionals, with the aim of developing new courses (University Degrees and Master's Degrees) backed up by research centres and research programmes. **Such educational and research actions must bring about new ways of addressing the risk of antimicrobial resistance.** They must also encourage new ways of sharing knowledge, for example with the development of Massive Online Open Courses (MOOCs) covering a variety of subjects (communication, life, human and social sciences). **This action would be part of the National Research Plan on antimicrobial resistance advocated by the "Research, Innovation and new medico-economic models" group and aim at organising social science research on this topic.**

The working group supports student initiatives in faculties of science that seek to present a particular topic in plain, easy-to-understand language and showcase interactive projects to a group of people outside of the university. These "open days" can be a constructive means of passing on information – and even training – with a different educational angle.

- Entertainment education

The educational scope of fiction and entertainment has long been taken on board in prevention campaigns in the US and Canada alike. **Entertainment education is a fun way of communicating specific knowledge** in terms of behaviour, prevention and so on, **via various recreational media**.

It does not set out solely to change perceptions, but also to trigger a change in behaviour by helping the general public to get a better grasp of specific issues. It can take different forms depending on the objective or audience in question.

Similar to the Norman Lear Center of the USC Annerberg School of Communication and Journalism (in Los Angeles),[64] **the working group recommends creating a documentary base supplied by academics and researchers that would be made available to production companies and scriptwriters who wish to use it for their production.** The database could be managed by academics specialising in communication as part of a cross-disciplinary approach (sciences and humanities). **The aims and practices of the media industry can be better aligned with the aspirations of public policymakers in this way.**

Moreover, video games are increasingly being used for educational purposes (e.g. courses taught in faculties of medicine). They can be tailored to children, adults/parents or healthcare professionals and, what's more, the development of digital aids for use in these types of programme seems to support their expansion. **Produced either by companies specialising in video games or by amateurs, each tool can become a powerful training means, from primary school right through to university.**

University and educational stakeholders could talk about building on these training and educational resources during European Antibiotic Awareness Day.

64 http://learcenter.org/

Research, innovation and new medico-economic models

The "Research, innovation and new medico-economic models" working group was tasked **with coming up with proposals regarding antimicrobial resistance research, particularly in order to encourage industrial research** for developing new antibiotics or new therapeutic strategies, as well as new diagnostic methods.

Two sub-groups were set up to suggest solutions for each problem :

- **"Research" sub-groups :** coordinated by Laurent Gutmann (INSERM), with support from the AVIESAN and AllEnvi research alliances, this sub-group suggested measures through which France could become a leading research stakeholder on bacterial resistance to antibiotics (Appendix 6).

  This sub-group brought together various stakeholders involved in French research on antimicrobial resistance with a view to identifying any gaps in France.

  The sub-group members drew particular inspiration from the work of the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) to draw up a National Research Plan on Antimicrobial Resistance.

- **"Innovation and new medico-economic models" sub-group :** coordinated by Florence Séjourné (Da Volterra), this sub-group worked on recommending concomitant measures for taking action at all levels to stimulate innovation.

  The working group brought together a panel of stakeholders involved in the development of innovative products: international pharmaceutical companies, biotech companies, associations of human or veterinary medicines manufacturers, healthcare professionals, patients' associations and public institutions. The group based its discussions on measures that already exist worldwide and that have proven to be effective.

  The working group particularly looked at measures set up in other countries such as the US, with the 2012 "GAIN Act", as well as work underway to improve this. Likewise, dialogue with the British "AMR Review" was ongoing to coordinate proposals. Lastly, telephone interviews were arranged with French and European agencies and institutions to come up with a clear set of measures that is complete, coherent and practicable.

State of play of research and innovation in France

France has the necessary scientific expertise to become a major player at international level, but it is being held back from being able to assert itself fully as one of the leaders in antimicrobial research by a certain number of limitations :

- **A lack of cohesion between R&D funding programmes in the field of antimicrobial resistance.** Of the 16 French government ministries, 9 are allocated funding and undertake action with the potential to contribute to research on bacterial resistance to antibiotics.[65] This dispersion is a result of a lack of coordination of research programmes and work, whether these be basic, technological, transitional, clinical, epidemiological or public health research activities. The health, environment and agronomy sectors are also inadequately coordinated on the issue of resistance, which restricts the overall assessment of this issue.

- The structuring of clinical research networks and epidemiological networks is poor, which represents an obstacle for the high-quality development of innovations: antibiotics and alternative therapies, diagnostic tools, vaccinations, epidemic risk controls of multidrug-resistant (MDR) bacteria and highly resistant bacteria (HRB).

- **Development of research & development towards and with low-income countries is poor**, while new resistance mechanisms (to even the most recent molecules) are emerging in these countries and spreading all over the world (e.g. carbapenamase NDM-1[66]).

- Economic models, both past and present, with little scope for innovation or investment in the field of bacterial infectious diseases in order to proceed from the proof of concept in laboratories to the clinical stage in terms of other therapeutic or pre-emptive areas (particularly cancer, metabolic and inflammatory diseases, AIDS, etc.), which without doubt require economic research to be undertaken.

- **The lack of research programmes whose development and innovation prospects could lead to alternative antibiotic strategies** such as the concepts of antivirulence, bacteriophages or molecules and biotechnology solutions which could be dedicated to risk control of the appearance and spread of resistance mechanisms and resistant bacteria (e.g. Eco-EvoDrugs[67]).

65 The Ministry of Foreign Affairs and International Development, the Ministry of Ecology, Sustainable Development and Energy, the Ministry of National Education, Higher Education and Research, particularly via the ANR, the Ministry of Defence, the Ministry of Social Affairs, Health and Women's Rights, particularly via the PHRC and other health research programmes, the Ministry of Agriculture, Agrifood and Forestry via the EcoAntibio2017 plan, the Ministry of Economy, Industry and Digital Data, particularly via the "Innovation 2030" fund for innovation.

66 Hammerum AM, Toleman MA, Hansen F, Kristensen B, Lester CH, Walsh TR, Fuursted K. Global spread of New Delhi metallo-β-lactamase 1. Lancet Infect Dis, Volume 10, 12 December 2010 pp.829-830

67 Baquero F, Coque TM, and de la Cruz F. Ecology and Evolution as Targets: the Need for Novel Eco-Evo Drugs and Strategies To Fight Antibiotic Resistance. Antimicrobial Agents and Chemotherapy, Aug. 2011, p. 3649–3660

Proposals for a National Research and Innovation Plan for combating bacterial resistance to antibiotics

With regard to challenges faced and the state of play in France, it is crucial that the country develop the means to better structure and coordinate research and development resources and programmes on antimicrobial resistance. This must contribute to the acquisition of knowledge at an internationally visible and recognised level, for the benefit of innovation. **The plan must also guide policy on human, animal and environmental antimicrobial resistance, both at an international and national level.**

Principles

Monitoring the evolution of bacterial resistance must be based on a consistent approach incorporating all of the dimensions of the research, development and innovation problems, by activating three levers:

- **monitor/control the use of antibiotics and biocides in all sectors** in order to reduce pressure on environmental selection;
- **slow down the appearance and spread of resistance mechanisms and resistant bacteria;**
- **speed up innovation in diagnostic, therapeutic and preventive tools for bacterial resistance and its spread.**

Only a so-called "One Health" concept, which does not separate humans from their environment (animals, food, soil, water, etc.) and which provides scope for optimal cross-disciplinary synergies, is likely to develop new channels for combating the appearance and spread of antibiotic resistance and for monitoring its effects. This approach requires a continuum between basic, translational, clinical, epidemiological and public health research (incorporating an economic dimension).

A research policy dedicated to combating bacterial resistance and reducing the use of antibiotics must form part of this effort to understand and monitor this phenomenon. **Such a policy must foster basic and environmental research and human health and veterinary research and development by encouraging and supporting the emergence of innovations up to the highest level of the TRL scale.**[68] It must also endeavour to anticipate human health risks and detect them as early on as possible, and firmly commit to achieving and maintaining the highest possible levels of international competitiveness and creativity. **Lastly, here, more than in other sectors, scientific interdisciplinarity and a holistic approach to research policy, is vital.**

Promoting research into antibiotic resistance **must be part of a long-term initiative**, from basic research up to patient and (human and animal) population level and their biological environments. **Basic research into antimicrobial resistance is the bedrock of diagnostic and therapeutic innovations.**

This National Research and Innovation Plan on Antimicrobial Resistance forms part of the national aim to reduce the use of antibiotics.

68 Technology Readiness Level

Governance

The national research and innovation plan for combating bacterial resistance to antibiotics must be coordinated in scientific and strategic terms, and the working group therefore recommends setting up two steering committees:

- **Strategic steering committee:** this will be in charge of defining the strategic guidelines of the plan. It will involve the key players in undertaking the action points, organise the implementation of these action points and oversee the running of the action points in accordance with a provisional schedule. **It will be jointly steered by the interministerial delegate and the Research Alliances, who will produce annual reports of the plan's progress to the interministerial committee.**
- **Scientific steering committee:** this committee, comprising key research stakeholders, will monitor the national plan. It will be chaired by the two research alliances involved in this topic: AVIESAN and AllEnvi. The research operators will first and foremost be members of these two alliances.

A plan based on two key measures that proposes tangible action points

Structure and coordinate research, development and innovation in terms of antimicrobial resistance and its effects

The aim of this first measure is to improve the visibility of (public and private) research bodies in France and also that of research programmes for improved organisation and development of international collaborations.

The objective is to organise and mobilise all of the means available, from research through to healthcare. This measure must facilitate synergies via collaborations, including with the private sector. It also seeks to stimulate competition and improve efficiency by avoiding replications between research projects. Lastly, this measure must create a unique gateway to specific models and the clinical network for manufacturers.

This measure is organised around several action points:

- **Identify all resources available** in the areas of basic, environmental, veterinary, clinical and transversal research, public health, human, economic and social sciences, including emerging manufacturers (SMEs and SMBs) and otherwise (pharma and veterinary manufacturers);
- **Build and maintain an open access data base of all funded research programmes into antibiotic resistance** (public and private) giving rise to a request for proposals in the last 5 years;
- **Reinforce translational, clinical and epidemiological research networks** dedicated to assessing diagnostic, therapeutic and preventive innovations and to controlling the epidemic risk of multidrug-resistant bacteria, based on existing operational structures of clinical and bacteriological units, in connection with European organisations, where these exist;
- **Establish bacterial resistance surveillance networks (human and animal) with low-income countries based on existing networks** (Aviesan Sud, Instituts Pasteur network, IRD, CIRAD, INRA, Fondation Christophe et Rodolphe Mérieux, etc.);
- **Set up and strengthen research networks and observatories to generate new** clinical, epidemiological, economic, societal and agronomic (veterinary and environmental) data at national level, relevant for new product research & development;
- **Jointly (academics/manufacturers) put in place regular exchange programmes by organising "academic/biotech/pharma" meetings** which could, for example, form part of the Rencontres Internationales Recherche (International Research Meetings) organised in partnership between Aviesan-AllEnvi and the LEEM, the Healthcare Industries Alliance for Research and Innovation (ARIIS)

and the French association for animal health industry (SIMV), the Public Investment Bank (BPI), **and could, in the long or short term, steer topics towards common issues leading to technological development or research interfaces;**

- **Support precompetitive/competitive projects and speed up transfer from the academic world to the industrial world using existing mechanisms** (Competitiveness Clusters, IRTs, SATTs, Institut Carnot).

Reinforce research and innovation efforts

It is necessary to follow a strategic plan for antimicrobial resistance research and innovation and improve the coordination of funding in France in connection with other existing initiatives, particularly at a European level.

The working group therefore recommends establishing a strategic plan for the next 5 years (2016-2020) based on a research framework programme for combating bacterial resistance.

This measure comprises several action points :

- **Adopt nine research priorities**: nine priority research fields have been identified (see the next page). Seven of them arise directly from the work of the Joint Programming Initiative to combat AntiMicrobialResistance (JPI AMR) which France has been heavily involved in. They must be incorporated into the programming of requests for proposals fully funded by France and by the European Commission. In addition, there are two other priorities: research towards and with low-income countries, and a public health research dimension by including research problems related to economics and human and social sciences. These priorities take into account challenges currently presented by bacterial resistance to antibiotics. Together, these priorities constitute an overall strategic approach which **will enable us to reduce the use of antibiotics and minimise the appearance and propagation of antibiotic-resistant bacteria and their resistance genes, as well as the consequences thereof;**
- **Support the involvement of French antimicrobial resistance stakeholders in international programmes/consortia**, particularly in the framework of the HORIZON 2020 European priorities;
- **Ensure France's financial assistance in European initiatives**, in particular the JPIAMR;
- **Prioritise bacterial resistance to antibiotics and antibacterial treatments in requests for research proposals funded by the various ministries in the course of the next 5 years;**
- **Implement a proactive policy of public-private co-funding** which supports the development of new products and technical solutions to proofs-of-concept in animals and humans;
- Encourage biotechnology companies to innovate and develop new solutions dedicated to combating antimicrobial resistance and its effects, by **the creation of an "antimicrobial resistance" fund and strategic guidance for high-risk projects.**

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	Priorities	Research/objectives
1	Improve known antibiotics and optimum use thereof during treatment, develop new antibiotics and alternative therapies (targeted immunotherapy, antibiotic adjuvant therapy to avoid resistances developing in accordance with the EcoEvodrugs concept, vaccination, phagotherapy, original and viable targets, etc.).	• Find new targets for antibiotics. • Develop new antibiotics. • Improve the pharmacokinetics and pharmacodynamics of neglected antibiotics. • Develop treatment protocols with existing and new antibiotic combinations. • Develop alternatives to antibiotics (vaccines, phages, etc.). • Incentives to minimise barriers to the development and introduction of new antibiotics and therapeutic alternatives.
2	Improve diagnosis and develop new (rapid) diagnostics for improved use of current antibiotics, new antibiotics and future alternative solutions.	• Improve existing, and develop new, diagnostic tools which allow us to more effectively distinguish between viral infections and bacterial infections. • Improve existing, and develop new, diagnostic tools which allow us to promote the use of narrow-spectrum antibiotics. • Improve existing, and develop new, diagnostic tools to identify antibiotic resistant bacteria, including their resistance profile. • Remove barriers which currently stand in the way of rapid diagnostic tests being accepted.
3	Establish a standardised international surveillance programme for bacterial resistance to antibiotics and the use of antibiotics in humans and in the environment (veterinary, etc.)	• Encourage research on the standardisation and extension of existing surveillance systems • Promote the development of a global surveillance programme, both phenotypic and genotypic. • Set up a global surveillance programme for the use of antibiotics, both in humans and animals and in the environment. • Responsible use of antibiotics.
4	Understand the inter-human transmission mechanisms of drug-resistant bacteria and resistance mechanisms among bacterial populations and the different reservoirs (humans, animals, environment, etc.). Translate this knowledge into evidence-based strategies to reduce the propagation of resistance.	• Determine by which mechanisms and how genetic resistance material can spread among bacteria and can circulate in human, animal and environmental microbial flora. • Determine whether food is an important vector for the spread of bacterial resistance. • Identify the effect of migration, tourism, different health systems, and veterinary practices in Europe on the spread of bacterial resistance. • Carry out an assessment of the risk factors which contribute to human exposure to antibiotics and multidrug-resistant bacteria. • Provide testable hypotheses for future clinical intervention studies and other studies that aim to control the appearance and spread of bacterial resistance. • Advance "macroscopic" predictions regarding epidemic phenomena of drug resistant bacteria such as have been seen in other areas, for example climatic phenomena. • Develop tools which could produce "microscopic" predictions for the dissemination of bacterial resistance to be made available in order to steer local policy on controlling these phenomena

5	Assessment of the contribution of "pollution" of the environment by antibiotics, antibiotic residue and drug resistant bacteria and their role in the spread of bacterial resistance, with the additional aim of establishing strategies for minimising environmental contamination.	• Understand the basic biological processes which underpin these phenomena in order to develop preventive and curative measures. • Identify the exact role the different environmental reservoirs (for example, surface water, soil, air) play in the appearance and dissemination of bacterial resistance. • Conduct studies in order to understand which transmission channels from the environment to humans are the most important in order to then minimise the spread of bacterial resistance. • Initiate meta-analytic approaches to national and international activities and their impact, which aim to reduce environmental contamination by human and animal waste involving the presence of antibiotics and drug resistant bacteria. • On the basis of these analyses, develop new systems contributing to reducing uses.
6	Epidemiological work (particularly in humans) for making the prevention and control of the transmission of bacterial resistance more effective.	• Launch international interventional research projects which aim to prevent and control the spread of bacterial resistance and can be tested in different environments (hospitals, community, etc.). • Compare bacterial resistance prevention and control practices in modular tests, taking into account their efficacy and economic cost. • Carry out research to identify and implement the best intervention strategies to reduce bacterial resistance in human and animal health and in the environment.
7	Assessment of the consequences of bacterial resistance to antibiotics.	• Attributable mortality and morbidity (including disability), and economic consequences. • Impact of public decisions on controlling bacterial resistance.
8	Research towards and with low-income countries.	• Specific factors influencing the appearance and spread of bacterial resistance in low-income countries. • Testing on the transfer of biotechnology innovations for the diagnosis and surveillance of bacterial resistance.
9	Research in human and social sciences and economics.	• Economic impact of bacterial resistance. • New economic models, particularly for antibiotic innovations. • Social and psychosocial determinants of antibiotic use practices and risk perceptions related to bacterial resistance.

Follow-up and assessment of the plan

The working group has come up with a set of process and performance indicators for assessing the setup and relevance of the action points set out in the plan over time:

Structure and coordinate:

- In a year's time, to have created a directory of public and private sector research stakeholders in the field of antimicrobial resistance;
- In two years' time, to have structured an operational clinical and epidemiological research network;
- In three years' time, to have set up a network between France and low-income countries;
- Build an open data base listing research projects on antimicrobial resistance;
- A number of clinical trials for innovative diagnostic, therapeutic and preventive products;
- A number of research projects submitted in requests for proposals with a cross-disciplinary approach;
- A number of collaboration contracts.

Reinforce research efforts:

- Amount of funding obtained by French research units at a national level within the JPIAMR and other European programmes;
- Annual number of specific and cross-cutting requests for proposals funded nationally and internationally;
- A number of projects funded nationally and internationally;
- A number of publications and patents coming from French teams;
- A number of innovative products undergoing clinical trials.

The medico-economic model specific to antibiotics is lacking in appeal

Over the last thirty years or so, only two therapeutic strategies or molecules have been developed in terms of antibiotic treatment. The lack of innovation is mainly due to **the low profitability of the economic model of antibiotics in relation to other therapeutic areas.** Indeed, antibiotics are inexpensive medicines, whose use is limited in time. The development of new molecules, however, is very expensive because of the technical and technological challenge posed by antimicrobial resistance.

Moreover, manufacturers are faced with a dissuasive paradigm: they are asked to develop new innovative antibiotics, which will nevertheless have to be used as little as possible since, to keep these new last-resort molecules effective, they will have to be distributed sparingly, and only in hospital settings.

This tense situation is only made worse by a regulatory and economic environment which does little to encourage innovation. Such a restrictive legal framework limits patients' access to certain innovative products that do not fall within the regulatory guidelines. On the other hand, with no clear definition, new alternative technologies to antibiotics cannot be assessed.

Finally, despite the research and development efforts that are likely to be made over the next few years, the specific ecological nature of antibiotics is still not sufficiently taken on board. The bacterial field is characterised by a strong link between human, animal and environmental health. **The many interactions between these different agents contribute to the occurrence of resistance, and this requires constant research and development regarding new therapeutic approaches.**

Advocate a series of measures to encourage investment and innovation

Various renowned economists have analysed this situation in-depth in recent years, and suggested several recommendations on how to resolve the problem of appeal for manufacturers in the field of innovation in the fight against bacterial resistance. **All of these stress the need to create a new economic model that would support innovation – from the development to the marketing stages – with political decisions to make on several parallel areas.**

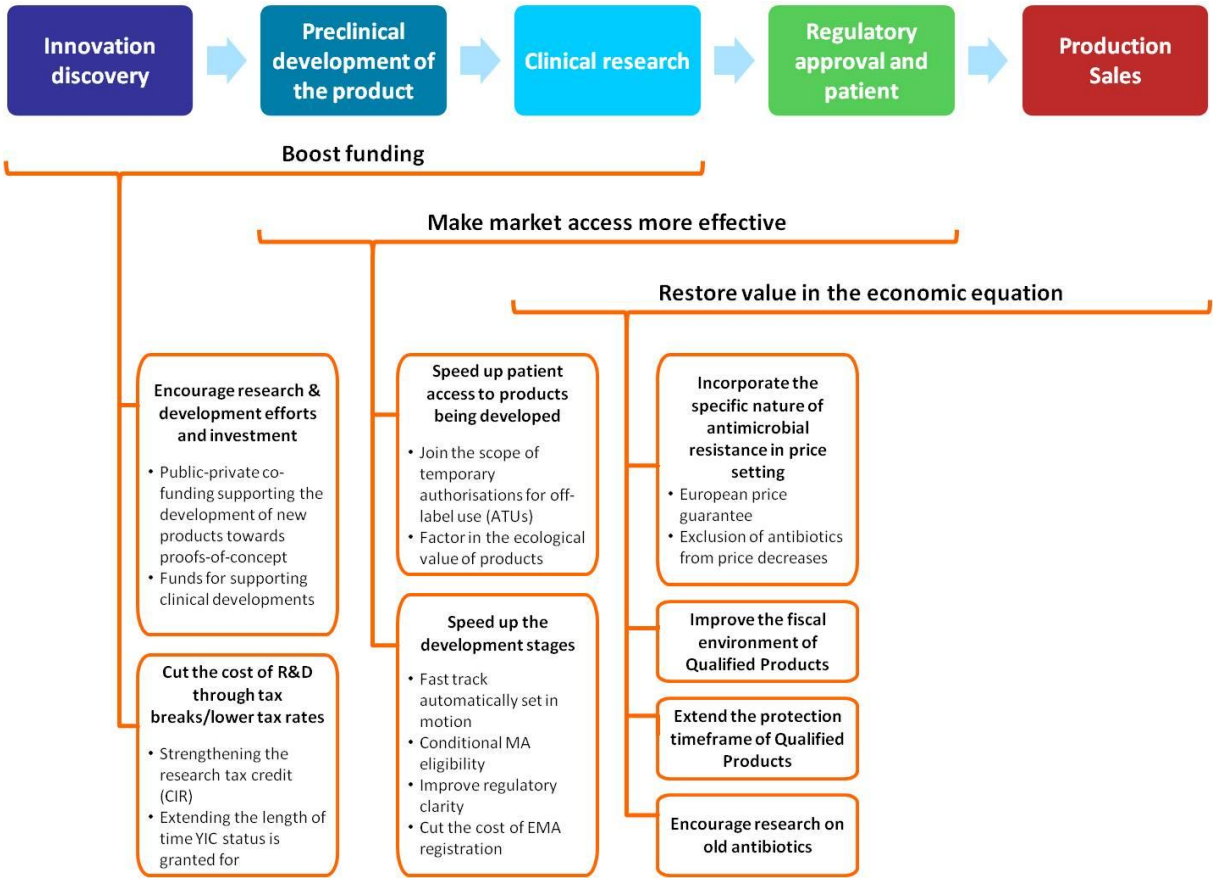
As such, the European Parliament's recent resolution on patient safety and antimicrobial resistance[69] considers that research is crucial on new tools for combating bacterial resistance. It urges the European Commission and Member States to come up with a legislative framework that encourages the development of such products.

The working group thus recommends a series of concomitant measures to support the research and development of products for combating bacterial resistance throughout the innovation value chain. We need to reduce the initial investment risk and increase the return on investment, as well as its predictability. Here are three ways in which development of innovations can be encouraged:

1. **Boost funding of research & development**
2. **Make development more effective for easier access to the innovative product market**
3. **Restore value in the economic equation**

69 REPORT on safer healthcare in Europe: improving patient safety and fighting antimicrobial resistance, Committee on the Environment, Public Health and Food Safety 4.5 2015: "Calls on the Commission and the Member States to accelerate research and development activities with a view to providing new tools to fight bacterial infections that are increasingly prevalent in Europe"

Acting on the whole innovation value chain:



Create a specific status for innovative products or technologies designed to combat antimicrobial resistance

The aim of setting up a specific status for innovative products or technologies designed to combat antimicrobial resistance is to provide a framework for the measures advocated. This tool must **pave the way for a series of incentives that provide a framework for innovative products, from the development to the marketing stages, and make the market more easily accessible for biological or technological innovations focusing on the risk of antimicrobial resistance appearing or spreading.** This specific status would apply for innovative products that comply with the following definition:

By "qualified product designed to combat antimicrobial resistance" we mean any product or technology for human or veterinary use which, alone or in combination with an antibiotic, can be used:

- to diagnose, prevent, pre-empt or treat any infection against which existing antibiotics are of limited efficacy, naturally ineffective or have become ineffective; or
- to reduce or limit the appearance and spread in humans, animals or the environment of antibiotic-resistant bacteria or antibiotic-resistant genes; or
- as an effective therapeutic or preventive solution for reducing or even replacing the use of an antibiotic.

The working group has come up with a series of recommendations for France, and proposes creating a version of the French "Produit Qualifié" (Qualified Product) status for the European Community. This would concern medicines for human health, medical devices, human or veterinary diagnostic tools and medicines for animal health. **The Strategic Council of Health Industries (CSIS) and/or Strategic Sector Committee for Health Technologies and Industries (CSF) will have to monitor these proposals.**

Boost funding for innovation

Research and development efforts and investment must be encouraged to stimulate innovation of Qualified Products. The working group recommends implementing ambitious specific tools, with significant funding and lower R&D costs through tax breaks or lower tax rates.

- **First of all a proactive policy must be set up for funding or jointly funding research and development projects focusing on innovative products.** This may be carried out through public-private partnerships[70] which support the development of new technical solutions or products towards proofs-of-concept in humans and animals. **The cost is around five to ten million euros per project, from discovery right through to the end of phase 1 clinical trials.** Another approach would involve setting up or giving precedence to French Public Investment Bank (BPI) funds that can support clinical developments until marketing. **Each new product would represent an investment of over 100 million euros.**
- **A further suggestion is to cut the R&D cost of Qualified Products through tax breaks or lower tax rates.** There are various tools in France for encouraging investment.

  The first is the Research Tax Credit (CIR), for expenditure related to projects to do with qualified products. The CIR is a strong incentive for small and medium-sized enterprises (SMEs) since it offers them concrete economic assistance in the form of funding for many businesses that still do not have any turnover since their products are at the development stage. It is therefore a highly appealing measure for SMEs, which represent a major driver of innovation and are key players in the fight

70 "Calls on the Commission and the Member States to strengthen incentives for public and private sector cooperation to reinvigorate antibiotic development R&D" – REPORT on safer healthcare in Europe: improving patient safety and fighting antimicrobial resistance, Committee on the Environment, Public Health and Food Safety 4.5 2015:

against bacterial resistance. **This would therefore involve, on the one hand, increasing the CIR rate when the R&D expenditure concerns R&D of qualified products, in comparison with the usual ratios** and, on the other hand, creating a "Senior infectious diseases physician" status, similar to the "Young Physician" status, with the same advantages. Accordingly, SMEs especially would be able to recruit senior industrial experts to conduct the clinical development of their own Qualified Products.

A possible second tool is the status of Young Innovative Company. Extending the status application length by three years for companies developing qualified products may be a real incentive for investment. The companies concerned should devote at least 25% of R&D expenditure to products combating antimicrobial resistance.

Make development more effective for easier access to the innovative product market

The working group recommends facilitating the development of medicines as well as medical devices that combat antimicrobial resistance through mechanisms that remove red tape and streamline and speed up the stages towards marketing, in France and Europe. This is because the time it takes to undertake conventional clinical development is at odds with the fast response times required in the face of bacterial resistance emergence. Given this lead time, a resolutely innovative approach calls for sound public/private cooperation.

- **To enable patients to access innovative products more quickly in France, it is recommended that Qualified Products be given priority consideration to be included within the scope of temporary authorisations for off-label use (ATUs).** This is a particularly appealing scheme specific to France, for it is aimed at making innovative medicines quickly available to patients in cases where the medical need is unmet but urgent.

  In addition, with a view to encouraging research, development and investment in antibiotic treatments with an ecological aim of combating bacterial resistance, **it would be worth assessing and attributing a value to Qualified Products that are being developed or coming to market as regards their potential contribution in terms of the selection or spread of highly resistant bacteria.** This is the case for antibiotics or combinations of antibiotics that present a similar efficacy profile to old antibiotics, but which have much less effect on the selection of resistant bacteria, as well as adjuvants or alternative strategies to antibiotics such as bacteriophages, antivirulence approaches or products that minimise the effects of antibiotics on microbiota.

  The group therefore recommends incorporating in Qualified Product development plans the need to include the proof that the product proposed will help to delay the selection of highly resistant bacteria and save the therapeutic classes most at risk from resistance today. This measure therefore has a long-term collective benefit in mind for patients. What's more, **for faster patient access in France**, a regulatory framework also needs defining whereby patients can have access to these available molecules (under clinical development or pending marketing) that have profiles corresponding to this prerogative of an "ecologically" beneficial product. **This measure would follow defined therapeutic recommendations but make up for the limits of clinical development via a standardised collection of microbiological and clinical data.**

  Lastly, these measures should be combined with a suitable strategy for setting prices and calculating the value of this collective benefit, which ultimately has a positive medico-economic impact overall. Establishing these new precursory concepts in the regulatory realm calls for very close collaboration between the different French partners (regulatory authorities, institutions responsible for defining the place of antibiotics in the therapeutic strategy, payer organisations, academics and industrial developers as well as scientific societies). **For that, a dedicated working group needs to be set up including representatives of all these stakeholders.**

- At the same time, **action within Europe is essential to create an environment conducive to the development of these qualified products.**

Upstream, the time it takes to examine Marketing Authorisation (MA) applications needs to be reduced by automatically setting a fast-track procedure in motion for Qualified Products. This is simple to put into practice, as it does not cost anything extra, and its importance has been highlighted by manufacturers. It aims at bringing Europe into line with American practices stipulated in the GAIN Act and which have seen **a rise in investment in the field.**

Similar to the French ATU, the EMA must enable new qualified products to have priority access to the conditional MA. At the same time, for veterinary innovations, setup of the future European regulations providing for limited-market MAs must be encouraged. **Finally, the group is in favour of the development of "adaptive pathways"[71] for clinical developments of qualified products.**

Today, there is a regulatory vacuum for a certain number of qualified products being developed. **Despite the EMA's efforts, work on improving the clarity and uniformity of European regulations for human health medicines and veterinary diagnostics must continue.** At European level, leadership is still lacking in this regard. France could play a role in urging Europe to pick up the pace of work underway. Accordingly, the regulatory framework for innovative therapeutic alternatives for which there are still no set guidelines would need clarifying. **In the same way, centralisation of product indications in Europe must be encouraged to harmonise names.**

On a final note, the cost of EMA registration must converge. **In this respect, the EMA should offer fee exemptions or discounts for Qualified Products, whether human or veterinary medicines.** Likewise, companies should be exempt from paying the costs of support processes. These measures aim at coming more into line with the GAIN Act and FDA policy.

Restore value in the economic model of products tackling antimicrobial resistance

To attract investors, it must be possible for them to make a sufficient return on their investment in a favourable regulatory, legal, fiscal and economic environment.

- **The specific nature of antimicrobial resistance must be taken on board when setting the prices of Qualified Products in medicines for human health.** As such, it is necessary to guarantee that future antibiotics and medicines intended to combat antimicrobial resistance will be assigned a European price, regardless of their Improvement in Medical Benefit (ASMR) level. **At the same time, national emphasis must be placed on measures that would concern protecting the price of medicines classed as Qualified Products.** All antibiotics (which means future antibiotics and antibiotics already on the market alike) must be excluded from widespread price decreases, such as in the context of Generic medicines monitoring committees. These national measures are easy and quick to implement, and will send a strong signal to manufacturers with an impact on the whole chain.
- **Improving the fiscal environment of Qualified Products is another measure at national level that could spark renewed interest in this field. This would involve introducing some pharmaceutical tax breaks (there are over ten taxes specific to the pharmaceutical industry).** First and foremost, the turnover of medicines classed as Qualified Products must be granted exemption from the convention-based discounts paid out under the safeguard clause L (article L.138-10 of the French Social Security Code). This action would form part of the framework agreement signed between the Leem and Economic Committee for Health Products (CEPS). The second measure would involve a contribution to the turnover of medicines (article L.245-6 of the French Social Security Code), by granting exemption for the turnover made for medicines classed as Qualified Products. Likewise, it is recommended that a deduction equal to 50% of the turnover made for medicines classed as Qualified Products be introduced regarding the contribution to be made to expenditure on promotion of medicines (article

71 "Calls on the Commission and the Member States to use 'adaptive pathways' schemes and other regulatory tools for earlier patient access to innovative antibacterials to treat resistant infections" – REPORT on safer healthcare in Europe: improving patient safety and fighting antimicrobial resistance, Committee on the Environment, Public Health and Food Safety 4.5 2015:

L.245-1 of the French Social Security Code). Both of these measures need to be passed under the Draft Social Security Financing Law (PLFSS). Lastly, the tax rate on products covered by patent licensing should be reduced.

- **Action must also be taken at European level to extend the protection of Qualified Products by making use of existing tools.** First, the protection period for MA data must be extended to 14 years, or even longer. This measure brings European practices into line with those in America, which have proven successful in attracting fresh investment to the field. It would therefore send a strong signal to investors and have a particularly strong impact in terms of communication, at no extra cost. For the protection of veterinary qualified products, the Proposal for a Regulation of the European Parliament and of the Council on Veterinary Medicinal Products currently being debated in the European Parliament must be supported: the rapporteur recommends conferring protection for 18 years on antimicrobials. **In the same way, protection must be extended by patents, and data protection for any new indication must also be extended, by extending the "8 + 2 + 1" rule by several years.** As such, after eight years of initial protection, plus two years of additional protection, the laboratory may ask for an extra few years of protection for each new indication. Finally, it is recommended that protection by patent law be extended by several years.
- **Protection of old antibiotics is also a necessity.** There is a great deal at stake as far as old antibiotics are concerned, for medicines that are still (or once again) of use to us are at risk of disappearing from the market because of profitability problems. **Here, it is not so much a case of stimulating innovation therefore, so much as shoring up a range of treatments that can effectively combat bacterial resistance by not obliging laboratories to stop producing a medicinal product of public interest simply because it is not profitable enough.** Insofar as use of such medicines is limited, **it would be worth setting up a working group to initiate cross-discussions between manufacturers, payer organisations and regulatory agencies so that fresh consideration can be given to the economic aspect of these old, but useful, antibiotics. The aim would be to ensure that some antibiotics – which are no longer profitable for manufacturers but which are nevertheless very useful for a limited number of patients – can remain available.**

Likewise, after a spell away from the market, a medicine loses its MA. **To avoid having to submit a new application to agencies, old antibiotics should be granted exemption from the MA sunset clause on public health grounds.** Lastly, additional protection must be granted for research on old molecules, along the lines of Paediatric-Use Marketing Authorisations (PUMAs). For veterinary medicines, this protection would concern any innovative finding that enables development of the MA for "old" antibiotics that are not covered by a protection period.

Rapid diagnostic tests are a special case, requiring specific action to encourage the development of qualified tests. We must begin by encouraging the development and assessment of tests via such French schemes as the "forfait innovation"[72] or Standard for innovative medical practices not listed on the general nomenclature (RIHN). Furthermore, the diagnostic industry must be given direct access to a registration and/or application submission procedure with the French National Authority for Health (HAS), and the value-added benefit of the test must be incorporated in the price that is set for the medical biology procedure. Lastly, development of Companion Diagnostics must be promoted by introducing economic advantages for their use (extending the period of market exclusivity for companion diagnostic tests to be paired with an antibiotic). **Similar measures must be taken for veterinary diagnosis[73].**

72 Innovation grant offering temporary, advance funding for an innovative procedure or medical device, subject to a trial being conducted aimed at supplying the missing clinical data

73 Veterinary diagnostics position paper: http://www.aefrv.eu/EC/2012/EMVD-Propositions-DG-SANCO-Final.pdf

Hold national discussions and support international action in favour of a sustainable medico-economic model for products that combat bacterial resistance worldwide

The working group's proposals aim at offering concrete, feasible solutions specific to France, even though the European context is inevitably given consideration. Through this approach it must be possible to put the various measures swiftly into practice to ensure a short- and medium-term impact. **That said, in economic terms they are still incomplete: the question of the medico-economic and societal value of innovative Qualified Products evidently needs further substantive work, with national discussions being held between the various organisations concerned (HAS, CEPS, DSS and CNAMTS) and manufacturers.**

French stakeholders must also take a stand in international initiatives on the subject to bring about a fully-fledged medico-economic paradigm shift for antibiotics, particularly last-resort antibiotics. The Resolution of the European Parliament encourages Europe and the Member States to take joint, international action, and particularly to take part in the **Global Innovation Fund** proposed by the Review on AMR, commissioned by the UK Prime Minister.

In this regard, it is worth noting the Review's radically different approach, **by considering the problem in its entirety with an international dimension rather than one specific to the country.** It outlines bold, ambitious solutions that are a far cry from those that have been advanced to date. These require, on the one hand, international coordination with international regulatory harmonisation – something which is difficult to achieve at present due to divergences between the US Food and Drug Administration (FDA) and the EMA. The Review particularly makes recommendations on antibiotic prices. **All of the solutions set out in the various economic reports on the subject talk of "de-linking" to manage the economic equation of new "last-resort" antibiotics.** The point is to replace a sales volume-based model with the guarantee of lump-sum payments, defined in advance, once a medicinal product has received approval – even if very little of the product is sold. **This solution thus guarantees revenue for manufacturers and enables them to make a return on investment.** Indeed, simple solutions of price adjustments do not go far enough in addressing the problem of low volumes of use with the use of the product being restricted to an often very specific group of people in order to keep it effective.

In order to guarantee a predictable financial benefit for developers, the method adopted by the UK Review is more ambitious. **It recommends setting up a global body, much like a global payer organisation,** with a broad base of buy-in from nation states, **to establish a mechanism to purchase the global sales rights to new antibiotics,** and to subsequently manage their supply internationally. **The development of the new product through to its marketing would still be carried out by the pharmaceutical industry, which would then surrender the right to market their new drug to the "global payer" in exchange for sufficient reimbursement to ensure an adequate return on their development costs.** The buyout figure is estimated to be two billion dollars per product that reaches the market. This solution tackles the economic problem and meets public health objectives.

The aim of this new body is to operate in the public interest. **Benefitting from total control over the product's marketing and supply, the "global payer" would ensure appropriate usage of the product worldwide based on unmet medical needs and emerging patterns of resistance.**

Another approach would involve granting "exchangeable vouchers" between products of a pharmaceutical portfolio to developers of new products tackling resistance. This measure particularly has pharmaceutical companies with extensive product portfolios in mind, for it would involve rewarding manufacturers that develop products for tackling antimicrobial resistance by offering them a certain number of advantages for their products under development. This type of measure has already been introduced in the US through the 2011 Creating Hope Act, **under which some companies benefit from a priority review voucher to secure marketing approval or a longer period of market exclusivity.**

However, these types of voucher pose various problems. First and foremost, their value would depend heavily on the size of sales for the top-selling drug on the market of the company receiving them. Second, this mechanism raises ethical issues, insofar as any drugs that are potentially of less value to society would not be submitted through the usual channels, slowing down the approval of other drugs designed for a greater medical need.

Antimicrobial resistance and the environment

The "Antimicrobial resistance and the environment" working group has been tasked with **making concrete, operational recommendations on the spread of antimicrobial resistance in the environment.** Their discussions focused on the phenomenon of bacterial resistance in its entirety, both inside and outside hospitals. This is because there are increasing numbers of hospitalised patients today who carry multi-drug resistance bacteria acquired in their day-to-day lives.

The working group brought together a range of stakeholders who pooled their expertise during five meetings between February and April 2015. **As complete a picture as possible was therefore painted of the observations underway in France on the theme of antimicrobial resistance in the environment.** In this way the scientists heading up these studies were able to present their findings and thoughts succinctly (Appendix 7).

The working group also referred to the conclusions of the workshop on antimicrobial resistance held during the national symposium entitled "Does our health depend on biodiversity?", which took place in Lyons on 27 and 28 October 2014 (Appendix 8). Note was also made of the assignment given to ANSES as part of the 2015 ecological transition roadmap (measure 56) on mechanisms involved in the development of antimicrobial resistance.

Lastly, recent progress made in governmental actions and deliberations at international level was also taken on board, especially the January 2015 joint interagency report by the ECDC, EFSA and EMA[74], the February 2015 Review on Antimicrobial Resistance[75] and the US National Action Plan adopted in March 2015.[76] The latter clearly takes antimicrobial resistance in the environment into account.

74 But the environment is not mentioned in this report. The European Commission indicates: "The Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report is the first joint report between the three agencies ECDC, EFSA and EMA on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. One of the findings is that improvement of existing systems should enable better integrated analyses in the future. To improve the integrated analyses, more detailed and comprehensive data are required. 1/ The European Medicines Agency … has … a pilot project to collect data on antimicrobial consumption by animal species. In the veterinary field, the Commission has already taken measures aimed at improving data collection. Commission Implementing Decision 2013/652/EU provides for harmonised monitoring of resistance within the food chain. 2/ The ECDC … will endeavour to collect data on antibiotic consumption in hospitals in more European countries. The Commission will use the information collected … to continue tackling the rising threats from antimicrobial resistance." See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp

75 "Review on Antimicrobial Resistance, Tackling Drug-Resistance Infections Globally" chaired by Jim O'Neill, February 2015: http://amr-review.org/sites/default/files/Report-52.15.pdf

76 "National Action Plan for Combating Antibiotic-Resistant Bacteria" The White House, Washington, March 2015: http://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf

Acknowledge bacterial resistance in the environment

Although we do not have any information telling us the exact extent to which each stakeholder (hospital, community medicine or veterinary use) is responsible in the rising phenomenon of antimicrobial resistance, one thing is certain today: **the mechanisms underlying the emergence, multiplication and spread of bacterial resistance to antibiotics are increasingly occurring outside of the conventional medical circuits.**

Indeed, **there are complex relations involved in the resistance selection process** stemming from:

- **Use of antibiotics outside of the medical setting,** such as in the case of self-medication by humans, veterinary care or the preventive use of antibiotics in intensive farming;
- **Storage and treatment (or lack thereof) of human and agricultural waste;**
- **Economic and social changes in the world's regions where antibiotics are produced,** nowadays very widely in emerging countries (India, China);
- **Global trade of live animals that carry multi-drug resistant bacteria as well as foodstuffs that may be contaminated by these micro-organisms;**
- **Discharge into the environment (soil, water, etc.) of diverse chemicals impacting the pressure of multi-drug resistant bacteria selection, such as heavy metals;**
- **Uncontrolled use of biocides for industrial and household purposes alike**, which contributes to antimicrobial resistance through the selection of resistances and/or adaptation of bacteria to biocides;
- **Human travel all over the world.**

For all that, antimicrobial resistance continues to be addressed primarily from the point of view of hospital medicine and hospital-acquired infections. This narrow approach has resulted in control policies that are struggling to curb the problem of bacterial resistance. **But, if the hypothesis that the current sources of antimicrobial resistance are exogenous to the healthcare system proves correct, the means to be put into practice must not be directed solely towards hospital settings.**

Measure the amount of antibiotics and extent of antimicrobial resistance in the environment

A more operational model for understanding antimicrobial resistance must be developed, for the fight against it must henceforth be organised so that the problem and its solutions are broached in their entirety. This includes usage, spread, exposure and transfer around humans and animals treated (as well as agricultural activities), and the environment, whether this be in developed, developing or emerging countries.

In this way, although the fight against antimicrobial resistance will continue to be waged for a medical benefit, since what is necessary is to safeguard the efficacy of antibiotics in treating patients with bacterial infections, the means to be mobilised to this end must be adapted to the purpose. **This calls for institutions and funding to operate in a new, coordinated and united way, released from the exclusive supervision of the ministries concerned by antimicrobial resistance.**[77]

Setting up a national antimicrobial resistance observatory

The group advocates the setup of a national antimicrobial observatory and development of workshop sites so as to standardise the markers for measuring the level of antimicrobial resistance in the main environmental compartments and chains of infection. This structure would be run jointly by the interministerial delegate in charge of antimicrobial resistance and the observatory director. Through this action, it must be possible to better characterise bacteria resistance in time and space, in terms of usage (veterinary, agricultural, hospital, community) and the different environments (soil, water). **The antimicrobial resistance observatory would thus be responsible for tracking and compiling the data acquired through selected markers, and for performing a regular analysis of antimicrobial resistance to track its development.**

In the same way, it would be worth this observatory having access to the list of prescribers having signed up to the Antimicrobial Stewardship Charter recommended by the "Responsible Antibiotic Use" group, so as to be able to create composite indicators. For example, antibiotic consumption, resistance level and the number of prescribers having signed up to the charter could be combined, over a restricted territory. **For educational purposes and to promote the efforts made at local level, the observatory could provide prescribers with maps and factsheets created from these indicators.**

Consider the effect of biocides on the occurrence of bacterial resistance

Lastly, the discussions and recommendations on biocide use must be taken on board alongside those on antibiotic use, both in terms of research and communication. This is because controlling the use of biocides is of major importance since it would help to limit one of the channels by which antimicrobial resistance can potentially be spread due to associated resistance phenomena.

77 See the US Government "Task Force", co-chaired by the Secretaries of Defense, Agriculture, and Health and including representatives from other institutions (Departments of Justice and Homeland Security, as well as the Environmental Protection Agency and the Office of Science and Technology Policy). It will receive particular guidance from the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria.

PART THREE

Working groups composition

Appendix

References

Working groups composition

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