



# ANTIBIO RESISTANCE



ŠSSFD



## Public Health & European Affairs

# Antimicrobial Resistance

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This policy paper formulates the propositions of pharmacy students from Slovenia, Czech Republic, Switzerland and France in response to antimicrobial resistance around Europe.



## Contacts

### France



**Chloé Lebbos**

Vice President of European Affairs

[affaires.europeennes@anepf.org](mailto:affaires.europeennes@anepf.org)

+336 38 55 61 33



**Marion Bouillot--Aubin**

Vice President of Public Health

[sante-publique@anepf.org](mailto:sante-publique@anepf.org)

+336 49 47 32 81



**Valentin Legrand Sourdillon**

Vice President of Professional Perspectives

[perspectives.profession@anepf.org](mailto:perspectives.profession@anepf.org)

06 43 63 29 38

### Slovenia



ŠTUDENTSKA SEKCIJA SLOVENSKEGA  
FARMACEVTSKEGA DRUŠTVA

**Špela Marzidovšek**

External affairs coordinator

[zunanje.zadeve@dsfs.si](mailto:zunanje.zadeve@dsfs.si)

+386 41 328 756

### Czech Republic



**Martina Krejčová**

President

[prezident@scsf.cz](mailto:prezident@scsf.cz)

+420 774 369 894



**Isabela Wheelanová**

PHC coordinator

[phc@scsf.cz](mailto:phc@scsf.cz)

+420 731 306 543



**David Brychta**

Policy coordinator

[policy@scsf.cz](mailto:policy@scsf.cz)

+420 602 874 397

### Switzerland



**Dhaval Srivastava**

Politics and Education

[dhaval.srivastava@asep.ch](mailto:dhaval.srivastava@asep.ch)

+41 79 552 96 33



**Fanny Mulder**

Vice President International & Exchange

[fanny.mulder@asep.ch](mailto:fanny.mulder@asep.ch)

+41 77 403 23 53

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## About our associations



### ANEPF, France

**ANEPF<sup>1</sup>**, the French National Association for Pharmacy Students, gathers **24 student associations** of all faculties of pharmacy in France, and thus represents **33,000 pharmacy students**. Its primary goal is to bring students' demands to the highest level in order to adapt to current challenges, with the aim of promoting interprofessionality and quality of care.

It also has various networks: **Public Health, Humanitarian, International, Tutoring and Industry**, which testify to the great involvement of tomorrow's generation of pharmacists in solidarity commitments, peer support and the distinction of our profession.

As a founding member, ANEPF administers the European Pharmaceutical Students' Association (EPSA), representing **160,000 students from 37 countries in Europe**, as well as the International Pharmaceutical Students' Federation (IPSF), representing over **350,000 students from 70 countries worldwide**. ANEPF also advocates for students through various networks and plateforme.

As with many other public health matters, ANEPF has been active in the fight against antimicrobial resistance (AMR) for many years. Indeed, it participated in the launch of **many public health campaigns** aiming students and professionals. It often organises **trainings and conferences** on the good practices of health professionals, publish **policy papers** targeting the french and international decision makers, and have recently put in place a **Hackathon** in collaboration with medical students and swiss pharmacy students, involving them in the fight against AMR. It started by the launch of a [MOOC](#) with 10 experts' testimonials to raise awareness among students. This was followed by the organization of a hackathon on antibiotic resistance, bringing together 64 students.

All the work resulting from this competition was used to draft [38 proposals](#) to the French government. The work was oriented around different axes: training for health professionals, human medicine, public health, social and societal innovation, medical and pharmaceutical innovation, the animal world and the environment.

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<sup>1</sup> <https://www.anepf.org/>



STUDENTSKA SEKOJJA SLOVENSKEGA  
FARMACEVTSKEGA DRUŠTVA

### ŠSSFD, Slovenia

The Students' Section of Slovenian Pharmaceutical Society (**ŠSSFD**) is a non-profit and non-political organization. Since 1975, its section actively helps students of the Faculty of Pharmacy, University of Ljubljana, to expand their knowledge outside the study programme and to contribute to their personal growth. It takes part in **national and international organizations** especially in the European Pharmaceutical Students' Association (EPSA) and the International Pharmaceutical Students' Federation (IPSF).

Students can participate in diverse projects. On motivational weekends, there are **soft-skills trainings and social gatherings**, and on competitions, students can **test their knowledge behind the pharmacy counter** or in a **simulated hospital department**. ŠSSFD organizes various humanitarian activities, public campaigns regarding current health concerns, symposiums and professional evenings, often in collaborations with other healthcare faculties, etc. All our projects are recapped in Spatula – the association's newsletter written by pharmacy students.

We are also highly involved with the **international community**. We offer many opportunities for our students to explore other countries and cultures. We are involved in programmes offered by EPSA and IPSF such as Twinnet, Students Exchange Programme (SEP) and Individual Mobility Programme (IMP) that provide work experience relevant for future employment.



### CzPSA, Czech Republic

The Czech Pharmaceutical Students' Association (**CzPSA**), is one of the two pharmaceutical students' associations in the Czech Republic and represents about **1,500 pharmacy students**. The mission is to supplement professional education and support professional growth of pharmacy students, defend their interests against the academic law or Czech pharmaceutical society, to facilitate the future placements of the members and represent members in Czechia or abroad.

The goal is achieved by organizing extension lectures, student scientific conferences, job fairs, soft-skill trainings or other cultural events.

**Fighting against AMR** is part of the agenda for many previous years. Besides other activities, CzPSA organizes **AMR public health campaigns** to support the proper handling of antibiotics in the society.



## ASEP, Switzerland

The Swiss Pharmaceutical Student association (**ASEP**), is a non-profit organization which was established in 1974 to promote and represent the interests of pharmacy students at a federal level, universities, professional associations and others in Switzerland. It aims to help pharmacy students establish contact with professional organisations in the various pharmaceutical sectors along with providing them with a voice and defend their interests in the political sphere.

ASEP is the only national pharmacy student's association in Switzerland and represents almost **1'500 members** of the ETH Zürich, University of Basel, University of Bern, University of Lausanne, University of Neuchâtel and the University of Geneva.

One of ASEP's major projects throughout the year is its **public health campaign**. The main goal of this campaign was to inform our students on public health and promote a healthy lifestyle that not only benefits their academic life but also their day-to-day activities. Therefore we promoted a lot of information about **drug abuse and mental health** since these are some of the issues most prevalent among the age group of the students.

ASEP is relatively new to AMR as most of the campaigns were handled by the national health authority but **feels the urge to help fight and raise awareness on AMR**. Recently, ASEP added microbiotic resistance to their public health campaign agenda and so collaborating on this policy paper would be the perfect way to kickstart our own campaign on the national level.

## Introduction

Antimicrobial resistance has been declared by the World Health Organization as **one of the top ten global public health threats** facing humanity<sup>2</sup>. The burden on European patients, healthcare systems and the economy is considerable. It accounts for approximately **33,000 deaths per year** and **€1.5 billion** in healthcare costs<sup>3</sup>.

The Covid-19 pandemic is an example of the disastrous consequences of an untreated pathogen. The cross-border nature of AMR means that **the European Union has a particular responsibility** to lead and implement a new, **ambitious, multisectoral response** to this growing phenomenon.

The Covid-19 pandemic has also been a revealing event in Europe's weaknesses as it has progressively shifted in its health competencies. Indeed, it accelerated the **institutional development of the European Health Union**. On November 11, Ursula von der Leyen announced the establishment of [a European Health Union](#), and the [Pharmaceutical Strategy for Europe](#), published on November 25, 2020. This strategy will contribute to the construction of a European Health Union by addressing long-standing weaknesses in the field of medicines, which the current Covid-19 pandemic has exacerbated and highlighted, and which affects equally AMR.

Since 2016, the fight against AMR as a priority for the European Union has taken a new turn. Following the [conclusion of the European Council](#) on the next steps in the fight against AMR, it now enters a **One Health approach**. It invites Member States to have an **intersectoral national plan**, with quantified objectives. The **One Health network** was thus born, becoming the seat of exchanges on **human and animal health policies**. Also, discussions with the **industry** are becoming more extensive, in order to **preserve access to existing antibiotics, strengthen research and develop innovation**.

Despite the recent momentum, increased willingness, and strengthened political commitment for a more coordinated, multisectoral approach to combating AMR, progress in developing and, more importantly, implementing national plans at the local level has not been optimal. To date, **60.4% of countries worldwide have developed national plans to address AMR**<sup>4</sup>, and of those countries that have not yet developed a plan, **33% of countries reported that a plan is under development**.

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<sup>2</sup> Ten threats to global health in 2019, WHO

<https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019>

<sup>3</sup> EU Action on AMR, European Commission

[https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance\\_en](https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en)

<sup>4</sup> AMR National Action Plans Study, december 2018

<https://epha.org/wp-content/uploads/2019/03/amr-nap-study.pdf>

Faced with the magnitude of this situation, the European pharmaceutical student network is committed to **raising large scale awareness and specifically to health professionals** through campaigns, but also wishes to **participate in the constitution of health policies**, both at national and European level. To do so, **students from France, Slovenia and the Czech Republic** have come together as part of member states of the European Union, each with different specificities depending on the cultural heritage of their health systems and government, resulting in different advances in e-health, public health and environmental health. The participation of the students from **Switzerland** allowed us to study a non-EU country, as well as gain from its experience in the fight against AMR. The interesting particularities of each of these countries will be detailed in the One Health national analysis of the antibiotic resistance phenomenon.

## Overview : Implementation of National Action plans

### France

Currently, in France<sup>5</sup>, AMR is the cause of **5,543 deaths per year** in patients with resistant bacterial infections. **124,806 patients per year** develop an infection linked to a resistant bacterium. **Antibiotic consumption is slowly decreasing** in healthcare institutions (-9.6% since 2015). It decreased by 18% from 2009 to 2019 in the city sector. But unfortunately, the consumption levels observed in human health in France remain 30% above the European average<sup>6</sup>.

As for National Action Plans, the French Ministry of Health adopted a National Antibiotic Alert Plan (2011-2016), based on the objectives of improving patient care efficiency, preserving antibiotics' effectiveness and promoting research.

However, the first inter-ministerial committee for health was devoted to the fight against antimicrobial resistance and led to the adoption in November 2016 of the interministerial roadmap for the control of antimicrobial resistance, which is part of a "One Health" approach.

The strategy is built around the fight against AMR in human health, with one of the objectives being to reduce antibiotic consumption by **25% by 2024**, in order to reach the European average.

Various bodies bringing together Ministries and health agencies are monitoring the progress of actions: the **inter-ministerial permanent restricted committee** dedicated to antibiotic resistance and the **steering committee targeting actions carried out in human health**.

Also, the issue of antimicrobials in the environment has been addressed in the report "Tous ensemble, sauvons les ATB"<sup>7</sup>, in the "Interministerial Roadmap for Controlling Bacterial Resistance to Antibiotics"<sup>8</sup> and in the "Roadmap 2015 for Ecological Transition"<sup>9</sup>.

<sup>5</sup> AMR, French Ministry of Health and Solidarities

<https://solidarites-sante.gouv.fr/prevention-en-sante/les-antibiotiques-des-medicaments-essentiels-a-preserver/des-antibiotiques-a-l-antibioresistance/article/l-antibioresistance-pourquoi-est-ce-si-grave>

<sup>6</sup> ECDC Data, [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(18\)30605-4/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30605-4/fulltext)

<sup>7</sup> Carlet and Le Coz 2015

<sup>8</sup> Interministerial Committee for Health 2016

<sup>9</sup> MEDDE 2015



## Slovenia

In 2016, **AMR level in Slovenia was below the European average** for most bacteria - 22,8% against 3rd generation cephalosporins, 0% against carbapenems for *Klebsiella pneumoniae*, and 19,6% against cephalosporins for *Pseudomonas aeruginosa*<sup>10</sup>.

The average **number of outpatient prescriptions** was 485 Rp/1000 people /day, most of which were prescribed to either children under 14 or elders over 65 years. Between 1999 and 2017, the **use of penicillins has dropped by 21%**, and the **resistance of S. Pneumoniae to penicillin has reduced by 51,8%**; the **use of macrolides has also dropped by 63,8%**, but unfortunately, **S.Pneumoniae resistance to them has increased by 140,7%**. A similar trend was noticed with **Fluoroquinolones**, where the overall use **reduced by 8,7%**, but the **resistance increased by 160%**.<sup>11</sup>

Section for antimicrobial treatment at the Slovenian Medical Association has proposed a [One Health approach for 2019-2024](#), which aims to **reduce outpatient use by 20% and hospital use by 10%**, **reduce regional differences**, focus on reducing the prescription of antibiotics for children, pay special attention to over-prescribers, etc.

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<sup>10</sup> Monitoring microbial resistance in human medicine, Expert consultation on European Antibiotics Day, 15.11.2018

[https://www.szpz.info/content/2018/posvetamr/Spremljanje\\_odpornosti\\_mikrobov\\_Ribic.pdf](https://www.szpz.info/content/2018/posvetamr/Spremljanje_odpornosti_mikrobov_Ribic.pdf)

<sup>11</sup> Antibiotic consumption in Slovenia and the rest of the world, Milan Čižman Tom Bajec Aleš Korošec [https://www.szpz.info/content/2018/podiplomskitecaj/Milan\\_Cizman\\_Tom\\_Bajec\\_Ales\\_Korosec-Poraba\\_antibiotikov\\_v\\_sloveniji\\_in\\_drugod.pdf](https://www.szpz.info/content/2018/podiplomskitecaj/Milan_Cizman_Tom_Bajec_Ales_Korosec-Poraba_antibiotikov_v_sloveniji_in_drugod.pdf)



## Czech Republic

The **prevalence of AMR is quite high in the Czech Republic**, reflecting the trend of resistance rates being **higher in eastern Europe**. The resistance rates for most antibiotics are not decreasing in any significant manner and for some, the rate is even increasing. **Surveillance of resistance** is done by a group called **PSMR**<sup>12</sup> (pracovní skupina pro monitorování rezistence), mainly focusing on **bacteria of respiratory and urinary tract infections**. Studies of resistance rates of *E. coli*<sup>13</sup> show little change between 2011 for most antibiotics, such as ampicillin (43 %), cotrimoxazole (24 %), ciprofloxacin (11-12 %), but higher rate in some antibiotics (amoxicillin (10,5 to 13,1 %), cefotaxime (2,1 to 3,8 %)) and an improvement only in nitrofurantoin (2,3 to 0,7 %). Between 2010 and 2017, the prevalence of *Streptococcus pneumoniae*<sup>14</sup> resistance to penicillin lowered (from 2,6 to 1,2 %), but a rise in prescription of macrolide antibiotics caused a rise in resistance to erythromycin (from 7,4 to 9,7 %).

The [National Antibiotic Programme Action Plan \(2011-2013\)](#), drawn up by the Central Coordination Group NAP in cooperation with the Ministry of Health, was built in Czech Republic on the principles declared in the EU Council Recommendation on Prudent Use Antimicrobial Agents in Medicine ([2002/77/EC](#)) and the EU Council Recommendation on Patient Safety, including the prevention and control of healthcare associated infections ([2009/C151/01](#)).

Following, the Czech Ministry of Health, in cooperation with the Ministry of Agriculture, has launched a new [National Antibiotic Programme covering 2019-2022](#), which will be aligned to the **One Health concept**.

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<sup>12</sup> <http://www.szu.cz/pracovni-skupina-pro-monitorovani-rezistence-psmr>

<sup>13</sup> Močová studie ATB rezistence, Žemličková H., 2016

<sup>14</sup> Surveillance antibiotické rezistence u *Streptococcus pneumoniae* v České republice, výsledky respirační studie za roky 2010–2017, Mališová L., Urbášková P., Jakubů V., Španělová P., Kozáková J., Musílek M., Žemličková H., 2019



## Switzerland

Up to this point, neither exact numbers nor precise scientific studies have been conducted on the repercussions of AMR, especially on the economic front. The only figures that are available are the number of **hospital contracted infections with almost reaching 70 '000**. There were also around **2000 deaths every year** according to Swissnoso (Nationales Zentrum für Infektionsprävention).<sup>15</sup>

Even though there has not been an effective monitoring of antibiotics and their resistance in the environment, there are **surveillance programs for other chemical products and substances** particularly when it comes to soil and water contamination. Therefore, it should be feasible to adapt these surveillance programs to monitor antibiotics and antibiotic-resistance.

The Swiss Confederation adopted a long-term national strategy in order to ensure the efficacy of the antibiotics. This strategy which is called **StAR**, Stratégie Antibiorésistance, not only concerns human beings but also **the use of antibiotics on animals and the environment**. These three areas are indeed in close contact and depend on each other. In order to obtain concrete results, **eight fields of action were established** : Surveillance (on the sale, use of antibiotics and their resistance), Prevention, Appropriate use of antibiotics, strive to fight against resistance, Research and development, Cooperation (between the different actors; doctors, veterinarians, pharmacists, Information and formation and general conditions (pertaining to studies, programs that encourage rational use of antibiotics) and finally framework condition and StAR newsletter veterinary medicine<sup>16</sup>.

To tackle the problem of antibiotic resistance that is exacerbated by the transfer of resistant genes between humans, animals and the environment, **the federal council launched another Programme with a more inter-professional and global approach** : "**Le Programme National de Recherche**" (PNR72): "La résistance aux antimicrobiens: une approche one-health." This programme began on the 24th of June 2015 and is based on a one-health model with the main objective of reducing the resistance to antimicrobial and their detrimental effects.

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<sup>15</sup> Stratégie Antibiorésistance Suisse, StAR

[https://www.blv.admin.ch/dam/blv/fr/dokumente/tiere/tierkrankheiten-und-arzneimittel/tier-arzneimittel/strategie-antibiotikaresistenz-schweiz.pdf.download.pdf/151118\\_Strategiebericht\\_StAR\\_F.pdf](https://www.blv.admin.ch/dam/blv/fr/dokumente/tiere/tierkrankheiten-und-arzneimittel/tier-arzneimittel/strategie-antibiotikaresistenz-schweiz.pdf.download.pdf/151118_Strategiebericht_StAR_F.pdf)

<sup>16</sup>

<https://www.blv.admin.ch/blv/fr/home/tiere/tierarzneimittel/antibiotika/nationale-strategie-antibiotikaresistenzen-star-.htm>

## Antibiotic Prescription

In Slovenia, **loose guidelines concerning antibiotic prescriptions contribute to the overprescribing of antibiotics for human and veterinary use.** Moreover, the national statistics record that broad-spectrum antibiotics are often prescribed without microbiological testing or even proper diagnosis. The fact that **between 25% and 75% of antibiotic prescriptions in long-term care facilities are inappropriate**<sup>17</sup> in terms of their indication, choice, dosage or duration of therapy, is of great concern. One of the key elements is also the **lack of large scale awareness** on how to properly use, store and discharge medicines.

### Testing prior to prescribing

As in Slovenia and in Switzerland, in Czech Republic, the use of antibiotics is regulated and a prescription is needed to receive an antibiotic, but overuse of antibiotics is still an issue<sup>18</sup>. **Not all doctors take the necessary steps to distinguish bacterial and viral infections.** In recent years **CRP test machines**<sup>19</sup> are becoming financially available to general practitioners, which allows them to diagnose bacterial infections more precisely. Many pediatricians also use **strep tests**<sup>20</sup> to diagnose Streptococcus pyogenes infections. In spite of this, the amount of antibiotics prescribed has not been going down and has even risen by 6% between 2013 and 2018.

### Unused medicines and automedication

Countries have **promising national systems of returning unused and expired medicines to local pharmacies**, which have to ensure their proper disposal, but according to recent observations, the systems still are not widely used. The problem of resistant bacteria is rising at an alarming rate and with it the need to find solutions.

**To limit automedication**, prescription medication in Slovenia can be dispensed only in pharmacies, and the pharmacist has to explain the correct use to the patient, which is also explained with a **sticker on the packaging**. Antimicrobial medications are prescribed with a prescription, and they must be **dispensed within 3 days** or the prescription will no longer be valid<sup>21</sup>.

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<sup>17</sup> Evidence brief for policy : antibiotic prescribing, WHO  
<https://www.euro.who.int/en/countries/slovenia/publications/antibiotic-prescribing-in-long-term-care-facilities-for-the-elderly>

<sup>18</sup>

<https://www.mzcr.cz/tiskove-centrum-mz/letosni-vysledky-sledovani-antibioticke-rezistence-potvrdily-vzrustajici-trend/>

<sup>19</sup> <https://www.nzip.cz/clanek/309-narodni-antibioticky-program>

<sup>20</sup> <https://www.tribune.cz/clanek/45221-zbytecne-predepisovani-antibiotik-zvysuje-rezistenci>

<sup>21</sup> <https://www.uradni-list.si/glasilo-uradni-list-rs/vsebina/2008-01-3730?sop=2008-01-3730>

## Guidelines

In a 2019 survey of medical professionals by ECDC<sup>22</sup> it was found that over **30 % of the Czech doctors have prescribed antibiotics they would prefer not to have prescribed** in the week before the study. **10 %** of the responding Czech doctors prescribed an antibiotic in the preceding week because they **were unsure of the diagnosis of the infection**. Some doctors even prescribe antibiotics **because it took less time than explaining why antibiotics were not needed**. 62 % of the surveyed healthcare workers (including professions other than doctors) answered all seven questions about antibiotics correctly; the average score was 6,48/7. However, there are concerns that this sample may not be representative of Czech healthcare workers<sup>23</sup> as a whole and that the real situation is worse than this survey may suggest. However, this survey shows the necessity of guidelines, mostly for the doctors who are unsure of the diagnosis of the infection.

**Guidelines for prescribing antibiotics** in Slovenia were provided by the National health insurance agency of Slovenia (ZZZS)<sup>24</sup> on the request of the National Commission for the Rational Use of Antimicrobials at the Ministry of Health.

There are **7 most common conditions where antibiotics are used**: upper respiratory tract infections, sinusitis, acute otitis media, pharyngitis / tonsillitis, bronchitis / bronchiolitis, pneumonia and cystitis. The guidelines were provided to help physicians decide when to prescribe. Given the frequent occurrence of above mentioned conditions, more efficient prescribing of antibiotics could reduce the total consumption of antibiotics in Slovenia, reduce side effects and costs, and most importantly reduce the resistance of certain bacteria. They describe the requirements and possible medical tests that should be performed before prescribing an antibiotic and also suggest the best choice of treatment. The recommendations weren't prepared for colds, nasopharyngitis, nonspecific upper respiratory tract infection, and viral pneumonia because antibiotics are not indicated for these infections and should not be prescribed<sup>25</sup>.

Some **common guidelines were also implemented in Switzerland** to avoid bacterial resistance ; an antibiotic should only be prescribed by an authorized professional when it is certain that the patient has a bacterial infection. When there is a possibility for another treatment which will cure the harm, then the other treatment should be chosen. Furthermore,

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<sup>22</sup> Survey of healthcare workers' knowledge, attitudes and behaviours on antibiotics, antibiotic use and antibiotic resistance in the EU/EEA, ECDC, 2019

<sup>23</sup> <https://www.tribune.cz/clanek/45221-zbytecne-predepisovani-antibiotik-zvysuje-rezistenci>

<sup>24</sup> <https://www.zzsz.si/en/>

<sup>25</sup>

<https://www.zzsz.si/ZZZS/info/gradiva.nsf/o/97495DBC5CA81679C12581E20034D545?OpenDocument>

anyone who is handling or prescribing antibiotics needs optimal training to deal with the treatment. Commissions of experts are actually developing recommendations on the use of antibiotics in the different domains of medicine. These recommendations are only developed in order to help professionals to give the correct treatment but it will not be controlled if they are correctly followed.

### Evaluation and indicators

In France, **indicators on antibiotic consumption** and antibiotic resistance in the city sector and in healthcare institutions are available via our [geodes](#) platform. For the first time in 2019, in order to have a more precise vision of antibiotic consumption in the city, Santé Publique France publishes, in addition to the usual indicator expressed in number of DDD, a **new indicator expressed in number of prescriptions**. The two indicators (DDD and prescriptions) were produced **for each year from 2009 to 2018**. They are broken down by antibiotic family, by territory (region and department) and by age group (8 in total).

The availability of these indicators makes it possible to better monitor and understand the evolution of antibiotic consumption in France thanks to an interactive display by territory, and identify its link to antibiotic prescription.

Their [study](#) underlines the **heterogeneity of antibiotic consumption according to age groups and territories**. In terms of trends and at the national level, while antibiotic consumption expressed in DDD has remained stable (22.5 DDD per 1,000 inhabitants per day in 2018), the number of prescriptions has decreased (-15%) and is evaluated in 2018 at 2.38 prescriptions per 1,000 inhabitants per day; this decrease is particularly noticeable among the youngest patients. The divergent evolution of the two indicators is mainly explained by a shift in cephalosporin prescriptions in favor of amoxicillin.

#### Proposals to member states :

- Access and promotion of digital and non digital tools including dispensing assistance software
- Development of indicators to document the success or failure of a therapeutic strategy
- Mobilize national agencies for behavioral studies of antibiotic prescribers
- Increased guidance and awareness on the consumption of antibiotics by pharmacists during dispensing
- Increased testing prior to the prescription of antibiotics

## Pharmaceuticals in Water

**Reducing the concentration of pharmaceuticals in the environment** has proven to play an important role in combating AMR. The main sources of environmental contamination by antibiotics is related to human activities : **discharges of treated wastewater** and the spreading of **sludge from wastewater treatment plants** and **livestock effluents**. Thus, antibiotics found in water are **more concentrated downstream** of wastewater treatment plant discharges than upstream<sup>26</sup>.

**Antibiotics, resistant bacteria and resistance genes** have the same sources of contamination. Concentrations of resistant bacteria and resistance genes decrease with distance from the source of contamination, whether it is a treated wastewater discharge or a land application site. Although wastewater treatment and land application treatments can reduce the amount of resistant bacteria and resistance genes released into the environment, they are not designed to eliminate them completely.

Work at ANSES<sup>27</sup> (*Agence Nationale de la Sécurité sanitaire de l'alimentation, de l'environnement et du travail*) in France has also looked at **environmental factors that could favour the selection of antibiotic-resistant bacteria and the transmission of resistance genes**. Few data are available on this subject. In general, it seems that the quantities of antibiotics found in the environment in France are too low to promote the survival of resistant bacteria and the persistence of resistance genes. In addition, the presence of **metallic trace elements or biocides**, the **diversity of bacterial communities** and the **heterogeneity of environments** could influence their fate in the environment.

As for the **health facilities**, the most persistent antibiotics are the most frequently quantified: **quinolones, fluoroquinolones, macrolides and sulfonamides ;  $\beta$ -lactamines**, the most widely consumed antibiotics, are rarely quantified in the environment due to their high degradability.

Water contamination from health facilities can come from different sources:

**The pharmaceutical industry** plays a big role in water contamination. For that matter, **Slovenian pharmaceutical companies** are legally obliged to ensure the treatment of wastewater.

Also, **hospitals** are responsible for some, through waste management coming from patients that show resistance to treatments, or the treatment of antibiotic waste. In **Slovenia**, the **lack of water treatment plants** is still an issue in hospitals, nursing homes and other facilities,

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<sup>26</sup> Un premier état de connaissance sur l'antibiorésistance, ANSES  
<https://www.anses.fr/fr/content/un-premier-%C3%A9tat-des-connaissances-sur-l%E2%80%99antibior-%C3%A9sistance-et-les-antibiotiques-dans-l>

<sup>27</sup> <https://www.anses.fr/fr>

where antibiotic metabolites find a way back into the environment through sewage, subsequently also emerging in drinking water<sup>28</sup>.

Also, in **Czech Republic**<sup>29</sup> wastewater **from hospitals** is identified as an important source of contamination and a possible source of antibiotic resistance as well. A new **wastewater charge and treatment from health facilities norm** was accepted in 2020, which tackles the previously insufficient water treatment in hospitals and other health facilities. However the norm is not binding yet. Other countries such as **Switzerland** did take action to tackle that issue.

For example, the Swiss Parliament adopted a **law for the protection of wastewater**. The goal of this law is to **eliminate micropollutants from this waterwater of Switzerland with the help of water treatment plants (STEP)**.

For **soil**, the main source of contamination by antibiotics comes from **animal waste** (of livestock given antibiotics) used as fertiliser and manure. They are then absorbed by water found at the surface (during rains) but remain at **lower concentrations than antibiotics prescribed for humans**. A study conducted by the *NAQUA in Switzerland (l'observation nationale des eaux souterraines)* on the presence of veterinary antibiotics in underground water around areas used for pig farming, found **small amounts of these substances in some samples (around 0.01 µg/l at most)**.<sup>30</sup>

But one thing remains certain, it is the **lack of information and research done on the development of resistance** through the environment. For that matter, the *French ministries in charge of health, agriculture and environment* have submitted a request for expertise on SLA and the environment to ANSES with a view to :

- Draw up an **inventory of current knowledge on the contamination** of different environmental compartments (soil and water) by antibiotics and resistant pathogenic bacteria.
- **Determine the mechanisms** underlying the selection and transmission of antibiotic resistance via the environment.

The results obtained are likely to **evolve with climate change and the development of practices related to the circular economy of water**, such as the reuse of treated wastewater or the artificial recharge of groundwater tables. These phenomena could indeed modify the routes of introduction and dissemination of antibiotics and resistant bacteria in the environment and have an impact on the capacity of the environment to dissipate these anthropogenic contaminants. In order to improve the comparison of data, ANSES (Agence Nationale de la Sécurité sanitaire de l'alimentation, de l'environnement et du travail, France) recommends that all studies on environmental antibiotic resistance should follow a set of indicators including antibiotics, a resistant bacterium and a resistance gene. The Agency

<sup>28</sup> <https://www.uradni-list.si/glasilo-uradni-list-rs/vsebina/2007-01-4695?sop=2007-01-4695>

<sup>29</sup> Revidovaná ČSN 75 6406, 2020

<sup>30</sup>

[https://www.bafu.admin.ch/dam/bafu/fr/dokumente/biodiversitaet/uw-umwelt-wissen/umweltziele\\_l\\_undwirtschaft.pdf.download.pdf/objectifs\\_environnementauxpourlagriculture.pdf](https://www.bafu.admin.ch/dam/bafu/fr/dokumente/biodiversitaet/uw-umwelt-wissen/umweltziele_l_undwirtschaft.pdf.download.pdf/objectifs_environnementauxpourlagriculture.pdf)

recommends that the studies that will be undertaken take into account the fate in time and space of these contaminations. Finally, ANSES makes recommendations to consolidate and deepen current knowledge on environmental contamination by antibiotics and resistant bacteria and genes, on the factors that promote their dissemination and on the assessment of the capacity of ecosystems to dissipate contamination.

Proposals to member states :

- To set up a systematic indicator measuring the evolution over time of antibiotic resistance as well as its cost and health consequences in terms of biosafety
- Strengthen the consideration of the environmental impact of a drug for the preparation of its marketing authorization file
- Mobilize national authorities to conduct environmental studies on the development of resistance within ecosystems
- Systematic review of the efficacy of the methods employed in order to be sure that they have an impact on the reduction of antibiotic resistance.
- Take into account the environmental impact of a medicinal production in the reimbursement of medicines

## Animal Health

Animals carry bacteria, which can become antibiotic-resistant due to the over-prescription or misuse of antibiotics. These resistant bacteria can later spread between animals and in their environments. In agriculture as well as veterinary medicine, these bacteria can **contaminate meat or other animal products** such as milk and eggs, but also through **animal waste**. Fruits, vegetables, and other products can become contaminated through contact with soil or water containing waste from animals.

In **France**, ANSES, through the National Agency for Veterinary Medicines (ANMV), **monitors the exposure of animals to antibiotics**. Since 2013, the **exposure of animals to critically important antibiotics has decreased significantly** and **has stabilized** over the last three years: between 2013 and 2019, it decreased by **86% for fluoroquinolones** and **94.1% for the latest generation cephalosporins**. **Colistin**, for which transferable resistance mechanisms have been described, has seen its exposure rate **decrease by 64.2%** from the baseline average level between 2014 and 2015.

Indeed overall, the number of **prescriptions of antibiotics given to animals is decreasing**. The quantity of antibiotics sold is constantly decreasing, with 422 tons of antibiotics sold in 2019 in France for example, 10.5% less than in 2018. However, the tonnage of antibiotics sold does not reflect the actual exposure of animals to antibiotics: this depends on the dosage of the drug, the duration of administration and the evolution of the populations of the different animal species under consideration. Taking into account the recommendations for use of the drugs studied and the estimated mass of animal populations, the **level of exposure is the lowest since monitoring began in 1999**. Compared to 2011, the baseline year of the [first Ecoantibio plan](#), which aimed to **reduce antibiotic use by 25% in 5 years**, **antibiotic exposure for all animal species decreased by 45.3%**. This decrease will continue in 2019, with an overall reduction of 10.9% compared to the previous year.

Also, Slovenia doesn't have significant problems when it comes to levels of antibiotics in meat. In 2013, the EU average was 110mg/PCU, while slovenian average was 22mg/PCU, representing a **significant decrease from 2010**, when the average was 46mg/PCU, meaning that veterinary use of antibiotics is not a significantly bigger factor than the problem of over prescribing them for human use.

In the **agricultural department**, the crucial steps of limiting ATB overuse in livestock have already been taken and a huge improvement has been made in the past decade, all over Europe. In Switzerland, this decrease is due to a ban introduced in 1999 which concerned the use of antibiotics for nutritional purposes and antimicrobial stimulators<sup>31</sup>.

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<https://www.blv.admin.ch/dam/blv/fr/dokumente/tiere/tierkrankheiten-und-arzneimittel/tier>

In Czech Republic, animals in general can only receive antibiotics with a veterinarian's prescription and feeding livestock antibiotics to promote growth is forbidden. It is also forbidden to use any antimicrobials in bees. Programs for eradicating diseases are an important part of Czech agricultural policies and are these measures improve the health of livestock and prevent them from being susceptible to infections from serious bacterial infections. These policies have proven to be effective – the use of antibiotics has gone down by 50% between 2008 and 2018. However there is still room for improvement with prescriptions of certain antibiotics, namely lowering the use of fluoroquinolones in poultry and 3th and 4th generation cephalosporins in dairy cows.

In Switzerland, a constant surveillance of new resistance is carried out in production of animal, meat and milk products.

As for veterinary use, many measures have been taken.

In Slovenia as well as Switzerland, antimicrobial medications must be prescribed by a veterinary doctor, and be dispensed within 3 days or the prescription will no longer be valid; they can be prescribed for a specific animal, or a group of the same species owned by the same person.

In Czech Republic, the prescription of antibiotics in general is individualised for particular animals in the herd. There is still an effort to increase the individualisation of therapy in pigs.

Proposals to member states :

- Political support for ecologically responsible agriculture

## Digitalisation

Health services all over the EU are gradually adapting to the digital era by introducing ePrescriptions and Patient summaries. **By 2025, both services will be implemented in 25 EU countries** (Austria, Belgium, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Slovenia, Spain, Sweden, Slovakia, Latvia, and Bulgaria) with the goal of ensuring the continuity of care for European citizens while abroad<sup>32</sup>. Numerous countries have already adapted the ePrescription system, and it has proven to be beneficial in ensuring proper patient care, as the **pharmacists can now access data about previously and currently prescribed medications**, check for possible interactions and even assess whether a correct medicine was prescribed.

In Slovenia, pharmacy services are upgrading, considering digitalisation and technical improvements - for example using **pharmacy robots**, which allows the pharmacist to spend more time advising the patient. The **e-prescription** has been mandatory since February 1st, 2016. Together with "Pregled uporabe zdravil" (Medicines use overview) and "Farmakoterapijski pregled" (pharmacotherapy overview), the e-prescription allows the pharmacist to **check previous therapy**, for example if a certain patient has been prescribed antibiotics frequently, and **detect possible interactions** between drugs or drugs and food. The e-prescription also ensures **easier communication between doctors and pharmacists** and issues **warnings for certain risk groups**<sup>33</sup>.

**The drug list system** in Czech Republic is the new tool for pharmacists to be more involved in patient's healthcare. With the permission of the patient, pharmacists have the possibility to **see all of the patient's prescribed drugs** during the previous year. Its aim is to prevent drug related problems and incompatibilities and it **opens doors to implement consultations** as a common part of pharmacist's work.

E-prescribing could also prove to be beneficial **when collecting data about over-prescribers**. One of the goals of slovenian One Health working group, which plans strategies regarding fighting AMR, is to **work with our national insurance company (ZZZS) to gather information** regarding doctors, who are prescribing antibiotics more often than average<sup>34</sup>.

The healthcare system in Czech Republic is also slowly undergoing digitalization. Since the beginning of 2018 **e-recept** (online medical prescription) has had an irreplaceable

<sup>32</sup> Electronic cross-border health services

[https://ec.europa.eu/health/ehealth/electronic\\_crossborder\\_healthservices\\_en](https://ec.europa.eu/health/ehealth/electronic_crossborder_healthservices_en)

<sup>33</sup> eReceipt, <https://www.nijz.si/erecept-0>

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[https://www.szpz.info/content/2018/podiplomskitecaj/Milan\\_Cizman\\_Tom\\_Bajec\\_Ales\\_Korosec-Poraba\\_antibiotikov\\_v\\_sloveniji\\_in\\_drugod.pdf](https://www.szpz.info/content/2018/podiplomskitecaj/Milan_Cizman_Tom_Bajec_Ales_Korosec-Poraba_antibiotikov_v_sloveniji_in_drugod.pdf)

role in the health system. It is mandatory to prescribe electronically for doctors unless unexpected situations arise or the medicine is not narcotic. The **e-recept system<sup>35</sup>** allows the Ministry of Health to monitor antibiotic prescription and warn doctors if they are prescribing too much antibiotics or overusing broad-spectrum antibiotics.

#### How does it work?

At a pharmacy, patients can submit a barcode or 12-digit code from either the prescription paper, text message, e-mail or the eRecept smartphone app. Since 2020, the patient's ID is also sufficient. The pharmacist then connects through these tools with the central repository of electronic prescriptions to dispense the right medicine. This innovation has many advantages, one of them is the possibility of **prescribing remotely**, which was highly utilized during the COVID-pandemic.

#### A non-EU country perspective

Switzerland's history with electronic information started in 1998, when a national strategy was put into place to bring several services into the digital age. Since then, in March 2017, the Federal Council passed a law calling for the setup of an electronic medical folder for patients. There is also a strategy in place from 2018 to 2022 to implement those medical records across several health institutions. The electronic medical record is meant to contain lab results, prescription history, radiology reports and can be easily modified by the patients themselves.

In terms of electronic prescriptions, **there has not been a nationwide system implemented** that is used by all healthcare institutions yet. Some projects such as the eMedication service were discussed in 2020 based on existing services like **EPR-XDS.b** infrastructures which were used to store medical histories of patients who could access and share them with other healthcare professionals. The eMedication service is designed to create a medication plan, alter it when needed, and stop at the right time along with the possibility of prescribing medication<sup>36</sup>.

Overall, each institution is free to develop their own electronic system and experiment with it in order to perfect it and serve as a base for other institutions to implement. One example would be [Presco](#) that is used for prescription purposes at the University Hospital of Geneva (HUG) to complement the electronic medical record and allows doctors to prescribe the correct medication with recommendations based on previous prescription history.

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<sup>35</sup>

<https://www.denik.cz/zdravi/cesi-plytvaji-antibiotiky-ministerstvo-chysta-kontroly-20181127.html>

<sup>36</sup>

[https://www.e-health-suisse.ch/fileadmin/user\\_upload/Dokumente/E/report-emedication-architecture-epr.pdf](https://www.e-health-suisse.ch/fileadmin/user_upload/Dokumente/E/report-emedication-architecture-epr.pdf)

## Digitalization and AMR

France has identified needs for the development of new data acquisition and processing technologies. The expertise conducted by the working groups and their synthesis have also identified scientific and technical needs that could open up vast fields of knowledge :

- **Development of digital tools for mass data processing** (e.g. "machine learning" and "deep learning" based on artificial intelligence) to analyze all environmental monitoring data and assess the risk of maintaining resistance as a function of exposure to ATB in different sites and situations.
- **Development of models to understand the interactions and transfers of ATB**, in the environment and of **predictive numerical tools** that would allow us to anticipate potential evolutions: climate change scenarios, effect of changes in water use practices, effect of action levers.

### Proposals to member states :

*We believe tracking overprescribers through the use of e-prescriptions would help to decrease the number of prescribed antibiotics. If we gather the information of the doctors who prescribe more than average, we could contact them personally and educate them about the importance of correct prescribing and following a protocol when it comes to antibiotics.*

*Furthermore, the e-prescription network could include warnings which would let the doctor/pharmacist know, when a broad spectrum antibiotic is being prescribed and suggest other possibilities for most common conditions. The network could have a separate section where only data about previous antibiotic treatment would be presented, that way the pharmacist could see if the patient is being prescribed a different antibiotic each time for similar conditions*

*Another thing to note is that the patient data sheet should include information on possible allergies and past adverse effects that the patient had reported - for example to reduce the number of allergic reactions to penicillin.*

- Integration of artificial intelligence to take into account the patient profile in decision making.
- Encourage formal research to document the success or failure of a therapeutic strategy.
- Development of an index specific to antibiotics, evaluating the environmental impact of their production cycle, as an aid to prescription.

## Prevention, Promotion

The general public is **not well-informed on the dangers of AMR**. This leads to incorrect use of antibiotics. This is most visible in the topical use of antibiotics. Many patients unnecessarily use antibiotic creams that they have at home (ei. leftovers from a prior prescription). These creams are often viewed as "nothing special" and patients often don't even realise they contain antibiotics. However, the use of topical antibiotics has been known to cause resistance for decades.

Simultaneously, in the report of 2018, the swiss population said that **they do not feel secured enough concerning their antibiotic treatments**. They feel like they do not have enough information about their treatment and the use of their medicines.

In France, the problem of antimicrobial resistance remains **relatively unknown**, according to a 2017 Ifop survey. 51% of respondents judge precisely what it is about (37% have heard of it but do not know exactly what it is about and 13% of the population has never heard of it). Of those who have heard about the problem, only 60% understand that bacteria become resistant to antibiotics (26% think it is people who become resistant to antibiotics and not bacteria, 11% think viruses become resistant to antibiotics).

Also, another possible way to decrease the incidence of resistant bacteria is **hygiene**. This method was used in the Hradec Králové hospital in the Czech Republic, where VRE (vancomycin-resistant enterococci) were a problem. After implementing better hygiene practices (especially hand hygiene), the **number of VRE infections went down drastically**. To overcome the problem of insufficient knowledge and better hygiene, it is of utmost importance to educate society and create a plan to efficiently tackle AMR, which can be achieved by means of public health campaigns, educational lectures and symposiums.

Finally, **waste management plays an important role** in the fight against AMR, and is often unknown by most of the population.

### National actions

A swiss national campaign has been launched in order to raise awareness in the population about antibiotic treatment and antibiotic resistance. This national campaign targeted the restitution of antibiotics with the slogan: "Antibiotique; quand il faut, comme il faut"<sup>37</sup>.

In 2019 the National antibiotic plan for the period 2019-2022 was approved by the Czech Republic government. It consists of three main pillars: improving the awareness of

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<sup>37</sup> <https://www.blv.admin.ch/blv/fr/home/dokumentation/nsb-news-list.msg-id-72860.html>

AMR and antibiotic consumption, control and prevention of AMR and support of science and research. Although it also includes a part about improving awareness and strengthening society's co-responsibility for maintaining the effectiveness of antibiotics and reducing the spread of antibiotic resistance, after two years not much visible action has been taken in this field. Expected outcomes are mass media campaigns for the general public, education of doctors and other professionals and support of vaccination programmes to prevent other infections.

**Safe disposal of medicines** in Czechia is ensured (for the general public) via pharmacies, where people can drop off unused or expired medicines for free. However a study in 2014 showed that only 52% of households are using that option and 24% of households don't follow safe disposal guidelines (throwing medicines away, flushing them down the toilet etc.). A Campaign called "**Medicines don't belong to the bin**" has started as a reaction by the State Institute for Drug Control. However the campaign hasn't had much success with no significant change in year-on-year comparison. With that in mind we see it a **necessity to educate the public further.**

In regards to AMR, the Action Plan of National Antibiotic Programme for 2019-2022 has set a goal of creating a mass media campaign focusing on the proper use and handling of antibiotics. The campaign should help lower the use of antibiotics therefore also lowering the antibiotics and its residues in our environment.

As European Antibiotic Awareness day (EAAD) takes place on the 18th of November every year, most of the awareness activities are also held on this day. State health institute prepares some graphics and organizes a press conference. At the instigation of Czech Chamber of Pharmacists, **pharmacists talk with patients about the correct use of antibiotics** more than ever and also cooperate with **pharmaceutical students who interview the general public with questionnaires from pharmacies.** This research has shown that people are slowly starting to differentiate viral and bacterial infections and its treatment and also do not request antibiotics from doctors. The effort dedicated to this week is not negligible but it should be expanded more throughout the whole year as in the aforementioned survey by ECDC from 2019 was found that only 30% of Czech healthcare workers has ever heard about EAAD.

### Student's associations actions

The slovenian Pharmaceutical student association ŠSSFD has organised their first **interprofessional congress** together with students of medicine and microbiology. The problem of AMR was presented from different points of view and the significance of the One Health approach was brought to light. ŠSSFD believes that this global burden, which encompasses overprescribing of ABs for human and veterinary treatments as well as its quantity in water due to lack of water treatment plants and inappropriate handling of

medicines, may be limited only by a collaboration of all crucial healthcare segments working together for better health.

The purpose was also to include all generations, so we launched a project for children, in which teachers would read an educational story about ABs to children. The project was later expanded into art education and lectures about hygiene.

ANEPF, the French National Association for Pharmaceutical Students, has also worked on a 4 level project to federate the students' and professionals' ideas and initiatives concerning a One Health Perspective on AMR. First, a MOOC was established with the help of pharmacists, microbiologists, infectiologists, veterinarians and environmental health professions, explaining the current situation and presenting the innovations being developed today. Afterwards, a Hackathon was put in place between Pharmacy students from France and Switzerland, and Medical students from France. From this hackathon, a large-scale public health campaign will be launched in 2021, and a policy paper was written with the student's strategies.

Every Antibiotic Awareness Week (18th-24th of November), the Czech Pharmaceutical Students' Association (CzPSA) collaborates with the Czech Chamber of Pharmacists to distribute questionnaires. These are handed out to the public in pharmacies and shopping centres. The respondent fills out questions on general antibiotic knowledge (ie. are antibiotics effective against bacteria, can antibiotics cause resistance) as well as questions about their usage of antibiotics (how many times were you prescribed antibiotics, how do you dispose of antibiotics...). The responses are digitized and sent to the Chamber of Pharmacists. During this week, CzPSA also organizes lectures about antibiotics for fellow pharmacy students.

Proposals to member states :

- Raise awareness from an early age, to antibiotic resistance. The objective is to reach a maximum number of students, and to increase the size of the target audience.

## Education

As it is part of their professional duty to take part in public health matters, health students are concerned by environmental issues. In order to provide concrete solutions to patients, it is essential to train health students to acquire new concepts and skills.

According to Article 55 of the Grenelle 1 Law<sup>38</sup>, enacted in France in 2009, initial and continuing education for healthcare professionals must include teaching on health issues related to the environment. Today, we note that these courses are not given in a homogenous manner to all pharmacy students in France.

Census of Environmental Health related to AMR Teaching in French Faculties of Pharmacy in 2020				
Environmental health related to AMR education at the undergraduate level	Environmental health related to AMR education at the graduate level	Environmental health related to AMR education in Elective Courses	Environmental health related to AMR education for Community Pharmacy students	No Environmental health related to AMR education
4%	8%	44%	20%	24%

*Results from a questionnaire sent to administrators of the 24 faculties in France - 22 respondents*

### Proposals to member states :

- Creation of a course on environmental health related to AMR in the common core of initial training
- Integration in health studies of a course in bacteriology, and around good practices concerning the use of antibiotics, as well as an optional course allowing students to work on concrete approaches to fight antibiotic resistance, common to all health students.

<sup>38</sup> [Article 55 de la Loi Grenelle 1](#)

## Call for action : EU Institutions

### The Pharmaceutical Production's impact on the environment

#### **Proposal 1 : Take into account the ecological impact of a medicinal production in the centralized market authorization file**

Recognizing that active pharmaceutical ingredients are harmful to the environment, the European Medicines Agency's (EMA) guideline on the environmental risk assessment of medicinal products for human use came into force in 2006. This guideline is in line with the Human Medicines Directive and applies to all new applications for market authorization. However, vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted as they are considered unlikely to cause a significant risk to the environment. In addition, there are specific guidelines for pharmaceutical substances for veterinary use and for pharmaceutical substances consisting of genetically modified organisms (GMOs).

The environmental impact is therefore **not taken into account in the benefit/risk balance of medicinal products for human use**. [Directive 2001/83/EC](#) requires the environmental impact of the medicinal product to be taken into account in the authorization process, but not in the benefit/risk balance. [Directive 2004/27/EC](#) clearly states that environmental impact should not be a criterion for refusal to market.

We therefore support the current initiative to take into account the environmental impact in the benefit/risk balance for human and animal medicines.

#### **Proposal 2 : Enhance the production of pharmaceutical raw material (RM) in Europe in a strategic manner in terms of location**

Some parts of the manufacturing process are now carried out abroad. This is the case for the production of active ingredients, and therefore of raw materials. As recently as 30 years ago, 80% of active ingredients of medicines authorized in the EU were produced in Europe. Today, this figure has been completely reversed<sup>39</sup>. In July 2020, the findings of the European Parliament are alarming<sup>40</sup>:

- **40% of medicines marketed in the EU come from third countries**
- 60 to 80% of active pharmaceutical ingredients are manufactured in India or China

<sup>39</sup> IGAS report, September 2013

<sup>40</sup> Drug shortage in the EU: causes and solutions

<https://www.europarl.europa.eu/news/fr/headlines/society/20200709STO83006/penurie-de-medicaments-dans-l-ue-les-causes-et-les-solutions>

- India and China produce 60% of the world's paracetamol, 90% of penicillin and 50% of ibuprofen

Various factors explain the industrial advantages of this relocation: a large number of drugs have seen the **end of their patents**, making them available as generics. In addition, social policies are driving prices down, encouraging low-cost production. Finally, **the almost non-existent environmental regulations in emerging countries**, like the size of their markets, have finally convinced manufacturers.

However, as the COVID-19 pandemic has highlighted, in times of health emergencies, and to meet the needs of European citizens, **dependence on these non-EU countries for raw materials is a source of shortages**. Thus, increasing the value of raw material production in Europe as much as possible for drugs of major therapeutic interest would make it possible to remove this dependence and to set up better coordination of production. This could be done by using the levers of fiscal and commercial policy to encourage the establishment in Europe of production sites for medicines and active pharmaceutical ingredients.

However, it is important that the clause of manufacturing in Europe does not affect the external market of the European Union, as well as the mechanism of international trade. Trade between EU countries accounts for two-thirds of the volume of the EU's trade activities and is of vital importance to the economies of all member states. However, **the EU is also the largest exporter and second largest importer in the world**, especially with the United States and China<sup>41</sup>. Another reason for this shortage is the fact that drugs of major therapeutic interest are often old, often public and not very profitable. So keeping this foreign market would compensate for this.

A **map of potential production sites** in Europe could be shared and worked on with the various national agencies of the member states. In addition, the possibility of setting up European public pharmaceutical establishments capable of producing certain medicines could be considered.

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<sup>41</sup> The European Union and its trading partners, European Parliament  
<https://www.europarl.europa.eu/factsheets/fr/sheet/160/l-union-europeenne-et-ses-partenaires-commerciaux>

**Proposal 3 : More regular internal audits of non-EU manufacturing sites by the EMA, EDQM<sup>42</sup> (European Directorate for the Quality of Medicines and Healthcare) or by competent authorities in the context of mutual recognition agreements**

**The pharmaceutical industry in the European Union maintains a high level of quality management** in the development, manufacture and control of medicines and their active ingredients. The European Commission is responsible for maintaining the harmony of legislation at European level. It adopts directives establishing the principles and guidelines of Good Manufacturing Practices (GMP) for medicinal products and similar products ensuring the quality of medicines produced by pharmaceutical companies<sup>43</sup>.

**Bilateral activities are usually conducted as part of a regulatory dialogue.** Mutual recognition agreements (MRAs) for GMP inspections allow for close cooperation with strategic partners. MRAs offer EU authorities the opportunity to **build on GMP inspections carried out by other regulators**, to waive the requirement to re-inspect products imported into the EU, and to share information on inspections and potential product quality problems. The EU has MRAs with Australia, Canada, Japan, New Zealand, Switzerland and the United States.

In the EU, all manufacturers of medicinal products for human or veterinary use **must hold a manufacturing authorization, whether the products are intended for the European market or for export.** For products coming from a third country, an inspection is required, unless the site has already been inspected in the three years preceding the application.

In order to reduce non-conformities, **internal audits** of production sites in third countries should take place regularly. Also an increase of these controls should be realized thanks to the increase of the actors able to carry out these inspections. In addition, **the inspection by actors coming from different horizons (countries/institutions) having a mutual recognition with the EU should be favored in order to limit conflicts and increase the scope of action<sup>44</sup>.** Thus, the multiplication of actors with common interests and values would increase the monitoring of sites<sup>45</sup>.

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<sup>42</sup> <https://www.edqm.eu/fr>

<sup>43</sup> Good Manufacturing Practices (GMP) for drugs, afmps  
[https://www.afmps.be/fr/good\\_manufacturing\\_practices\\_gmp\\_ou\\_bonnes\\_pratiques\\_de\\_fabrication\\_bpf\\_des\\_medicaments](https://www.afmps.be/fr/good_manufacturing_practices_gmp_ou_bonnes_pratiques_de_fabrication_bpf_des_medicaments)

<sup>44</sup> The Inspection Programme | EDQM - European Directorate for the Quality of Medicines.  
<https://www.edqm.eu/fr/Programme-inspection-cep-DEQM-159.html>.

<sup>45</sup> La qualité de la chaîne du médicament à l'heure de la mondialisation, Ordre national des pharmaciens  
<http://www.ordre.pharmacien.fr/content/download/122408/639818/version/6/file/Cahier+th%C3%A9matique+4+-+La+qualit%C3%A9+de+la+cha%C3%Aene+du+m%C3%A9dicament.pdf>

#### **Proposal 4 : Revise Good Manufacturing Practices (GMP) by incorporating environmental monitoring**

The EMA supports the European Commission's activities in China, India and Russia, contributing to interactions on pharmaceuticals between the EU and the regulatory authorities of these countries<sup>46</sup>. **EMA's activities aim to help China implement Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) standards** similar to those applied in the EU, in order to:

- facilitate the use of products and data from China;
- **to achieve a comprehensive approach to long-term drug manufacturing and monitoring.**

It is also essential to add **environmental considerations**. Indeed, the environmental standards of production sites outside the EU are considerably lower than those imposed within the European Union. This has been the partial cause of the relocation of European industries, and the cause of the amplification of environmental and public health problems, such as antibiotic resistance. Currently, 90% of antibiotics consumed in France are manufactured by Chinese or Indian factories. **In some regions of India, the concentration of antibiotics in water is in the order of one milligram per liter, which is 100,000 to 1 million times higher than in Europe.**

#### **Proposal 5 : Develop a label to indicate the European pharmaceutical laboratories that have adopted an eco-responsible production method**

The legislation approved by parliament on banning the use of plastics by 2021 includes mandatory labelling of the negative environmental impact of cigarettes containing plastic filters that are discarded on the street, as well as other products such as plastic cups, wet wipes and sanitary napkins. The agreement also provides for a **strengthened application of the "polluter pays" principle**, particularly for tobacco, through the introduction of extended producer responsibility.

Being aware that the imposition of environmental standards is an important economic constraint and encourages the relocation of industries, but that it remains important to put in place measures to limit the ecological footprint of industries, we believe that a system of **rewarding measures taken by industries** should be considered, under the same model as the one mentioned above. The implementation of a label for European pharmaceutical laboratories using eco-responsible methods would be interesting to develop.

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<sup>46</sup>China, European Medicines Agency <https://www.ema.europa.eu/en/partners-networks/international-activities/bilateral-interactions-non-eu-regulators/china>

## Good practices & Prescription of Antibiotics

### Proposal 6 : Harmonization and European transposition of responsible prescribing tools such as the PBT index<sup>47</sup>

Medicines are an important health product in the healthcare system, but they can have a very negative impact on the environment. The pharmacist, as a drug specialist, is the first person involved in the fight against drug pollution. In France, he acts as the collection point for unused medicines and waste from healthcare activities with infectious risks. Unfortunately, this is not enough and one of the ways forward would be to **develop the pharmacist's field of actions.**

The pharmacist could **substitute a drug with a lesser environmental impact than the drug initially prescribed for an identical medical service rendered with the agreement of the prescriber.** This substitution can only be possible if the pharmacist has data to guide his or her choice and if the prescribing physician gives his or her agreement based on the patient's file.

A tool should be made available to pharmacists in a generalized manner: The **Persistence Bioaccumulation and Toxicity (PBT)**. The PBT is an index that takes into account the **persistence** of the molecule in the aquatic environment, the **bioaccumulation** in aquatic organisms and the **toxicity** with respect to these organisms. Each criterion is scored from 0 to 3 and then they are added together to obtain a value that varies from 0 to 9, 0 being the value for a molecule that is the most virtuous for the environment and 9 a molecule with a very high impact.

Since 2013, the PBT index has been indicated in Sweden for **each drug in the paper therapeutic booklet made available to the prescriber.** This allows the prescriber to choose the molecule with the least environmental impact for equivalent indications and efficacy. The **environmental data are provided by the Swedish Pharmaceutical Industries Association (ILF)** and studied by the Swedish Environmental Research Institute. Its use is extended to all Sweden since 2010.

The PBT is also used to define the environmental profile of establishments, including the study of the 50 most prescribed active substances in volume. A study was conducted in the Portes de Camargue hospitals in Tarascon, France : 12 AS do not have a complete PBT, 10 AS are absent from the list. Several elements can be drawn from this: first of all, the need to transpose this index for a European use, since it only takes into account 58% of the listed molecules in France. Moreover, only the active ingredients are evaluated. An **integration of**

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<sup>47</sup> Contribution Santé environnementale ANEPF  
<https://drive.google.com/file/d/1T1XyuBFdqYSgo6R8R5eF9eMb-wQlThW9/view>

**excipients** in the measurement of this index would allow a **broader vision of the toxicity of the drug**.

Requiring **transparency of the composition of active ingredients of drug products by the industries to public authorities** as mentioned in the Pharmaceutical Strategy for Europe is necessary for the development of this kind of tools, in order to facilitate the study of their environmental impact and allow innovation. In addition, the **financial and human resources of the European Union must be involved in the transposition of this tool on a European scale. of this tool on a European scale.**

### **Proposal 7 : Conduct studies on unit-dispensing of antibiotics by the EMA and statistically between Member States**

Unit dispensing is already practiced in many countries, including in Europe (United Kingdom, Netherlands, Czech Republic). This method seems to **promote the proper use of medicines, reduce waste and the cost of packaging in blister packs/boxes**.

In the context of antibiotic treatment, unit dispensing has also been mentioned as a way to **reduce the risk of bacterial resistance linked to self-medication** (with leftover prescriptions) and to the **disposal of surplus tablets in household waste or toilets**.

It could also have an **educational impact** on the population and help reduce the increase in antibiotic consumption observed in France in recent years.

To assess the impact of unitary dispensing of antibiotics in terms of reducing waste, protecting the environment and improving compliance with treatment, Inserm<sup>48</sup> recently conducted a study in four French regions. A larger scale study is needed to respond to the urgency of the situation and to encourage the different Member States to study unit-dispensing at their national level. Finally, coordination of these studies by the EMA would facilitate data processing and a large-scale comparison in order to have a clearer vision of the benefits and risks of unit dispensing.

### **Proposal 8 : During the European Antibiotic Awareness Day, ask countries to present a report of their initiatives and good practices, which would then be taken up by HERA for analysis and transposition at the European level**

The European Commission is considering the creation of a **Health Emergency Response Authority (HERA)**. It should allow better coordination in the face of cross-border health threats. Its creation will be proposed by the end of 2021 and it will be operational in 2023.

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<sup>48</sup> <https://www.inserm.fr/>

As antibiotic resistance is both an urgent health priority and a cross-border threat, it has a rightful place in HERA's policies. Also, the establishment of a centralized coordination would allow an increased reactivity by the European transposition of national initiatives exposed through the AMR One Health Network, or on the European Antibiotic Awareness Day. It would also allow a better assessment of the situation by the study of national data of each Member State.

Inspired by the American BarDA (authority for advanced research and development in the biomedical field), one of the missions of this authority would be to negotiate public-private partnerships with pharmaceutical companies and research organizations. This mission could be developed to stimulate innovation in antibiotics.

### **Proposal 9 : Making digital health systems interoperable in Europe in order to use this tool as a means of improving therapeutic adherence.**

With the democratization of digital health in Europe, it seems essential to move towards an increasingly personalized medicine in terms of antibiotics. The prescriber, from **his digital services space**, could have access to an **Artificial Intelligence analyzing his patient's medical file**, while respecting medical secrecy. It would analyze, for example, the patient's medication history, antibiotic susceptibility tests, biological analyses such as ECRU or the status of the last antibiotic-based therapeutic strategy (failure or success). In the long run, this could guide the prescriber towards the antibiotic that promotes the least possible resistance in the patient in question.

This would be a **de-standardization of recommendations** and a step forward towards **personalized medicine**. We could also imagine optimizing the patient's profile by providing a screening of his or her bacterial flora. With this technology, we could move from probabilistic antibiotic therapy to precision antibiotic therapy.

### **Proposal 10 : Expand and update the guidelines for participation in CPD for healthcare professionals.**

These guidelines, released in 2017, capture a panel of practices, separated by profession. However, an evolution of the roles of each health actor has taken place, notably through the organizational upheaval that was the COVID-19 pandemic. Thus, it would be interesting to rework these guidelines, and to detail more broadly the different fields of action of each profession, illustrating them with examples of practices in different EU countries. Including all sectors of the One Health approach on AMR is today necessary in order to raise awareness and to promote interprofessional collaboration.

Also, hygiene measures such as systematic hydroalcoholic solutions in public places and in medical establishments could be added in those guidelines, as those measures have helped decrease the number of seasonal infections, and therefore the use of antibiotics.

**Proposal 11 : Promote the pharmacist as a central player in the regulation between the prescription and the taking of antibiotics by making him the n°1 coordinator in the fight against antibiotic resistance.**

As for awareness of the proper use of antibiotics, prescribers often do not have the time to adapt the prescription to the needs and customs of the patient. Also, the pharmacist is the drug specialist, which makes him a major asset in the choice and administration of the treatment. However, in several European countries, the **pharmacist is an isolated player**.

**Antimicrobial Stewardship (AMS)** can be described as a set of defined, multidimensional, structured, and integrated measures to ensure appropriate and safe antimicrobial use to improve clinical outcomes and minimize the further development of antimicrobial resistance.

Global patterns of antimicrobial resistance vary considerably and these trends are constantly evolving, so health care teams have had to evolve and adapt, with **pharmacy increasingly leading and participating in local activities, national and global antimicrobial resistance activities**.

Between 2003 and 2006, the UK Department of Health (now the Department of Health and Social Care) invested significant funds in this area, enabling the expansion and emergence of new roles for pharmacists, which coincided with the development of more defined antimicrobial resistance action plans across the UK. Since then, the role of antimicrobial pharmacists has become well established, along with their formal recognition as members of multidisciplinary AMS teams in secondary and tertiary care settings in England. Similar roles have also evolved in Scotland, Wales and Northern Ireland.

As a result, **many antimicrobial pharmacists play a key role in multidisciplinary advisory committees and antimicrobial stewardship teams at the local, regional, and national levels**. A better understanding of the range of pharmacy skills and activities undertaken within the AMS would be valuable in further developing what pharmacy offers and exploring opportunities to increase its impact in all settings and fields.

AMS activities in pharmacy are antimicrobial prescribing reviews and evidence-based medication optimization, as well as by conducting audits and feedback as part of the pharmacy team's standard work routines. Pharmacy professionals may also be involved in the development, review, and implementation of AMS policies and guidelines, in advisory roles, and in the education and training of other healthcare professionals, patients, and the

general public. It is very likely that these roles have not been developed or expanded to their full potential; further integration of pharmacy teams and infrastructural support (e.g., funding) were suggested as essential steps to improve positive outcomes.

Implementation of AMS initiatives in secondary care is essential; they can help optimize antimicrobial therapy and improve patient outcomes while reducing the burden of hospital-acquired infections, the spread of antimicrobial resistance, and associated healthcare costs.

Pharmacy's Role in Antimicrobial Stewardship (AMS)<sup>49</sup> :

- Development, review and implementation of AMS guidelines and policies;
- Clinical advice to optimize antimicrobial prescribing and use;
- Monitoring, auditing and feedback;
- Education and training of health care professionals, patients, and the general public;
- Development, testing and implementation of AMS digital platforms, including e-prescribing, smartphone apps, and e-learning;

There is potential to further develop the role of pharmacies, provided appropriate integration and infrastructural support is in place, a development necessary to improve health systems coordination, particularly in the fight against antibiotic resistance.

### **Proposal 12 : Democratize the evaluation of prescribing practices within the Member States by developing a European "responsible prescribing" label for human and veterinary prescribers**

As shown by the EPHA evaluation of national measures concerning antibiotic resistance, **one of the common measures taken by the EU countries is the reduction of antibiotic prescription**. This requires first of all the **identification of bad and over-prescription**, and the adjustment of practices. This cannot be done without an evaluation of prescribing practices in the Member States.

In Slovenia, weak guidelines on antibiotic prescribing contribute to the overprescription of antibiotics for human and veterinary use. To counter this phenomenon, a case-by-case evaluation system has been put in place. Electronic prescribing has proven to be beneficial in collecting data on overprescribers. One of the goals of the Slovenian One Health working group, which is developing strategies to combat antimicrobial resistance, is to work with the national insurance company (ZZZS) to collect information on physicians who prescribe

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<sup>49</sup>Liaskou, M., Duggan, C., Joynes, R. & Rosado, H. R. author H. Pharmacy's role in antimicrobial resistance and stewardship. The Pharmaceutical Journal  
<https://pharmaceutical-journal.com/article/research/pharmacys-role-in-antimicrobial-resistance-and-stewardship>.

antibiotics more often than average. Feedback will be given to these prescribers, which will be non-punitive and non-guilty.

Thus, promoting these evaluations of practices at the national level would allow a democratization of their realization by the Member States. Also, **centralizing these data at the European level would make it possible to promote good practices and accelerate their readjustment through reinforced transnational cooperation.**

### **Proposal 13 : Promote the mobility of healthcare professionals to develop knowledge of different practices**

As health practices are national competences of the Member States, they differ, especially regarding antibiotic prescription in human and veterinary medicine, and all the related practices that impact the development of resistance (patient support, e-prescription and teleconsultation, environmental standards, waste management, etc.). **Sharing these practices, comparing the consequences and results,** would ensure an evolution towards innovation and optimization of our systems.

Working groups and consultations have been set up, including the **AMR Stakeholder Network**, hosted by the European Commission's Health Policy Platform and led by the European Public Health Alliance (EPHA), which is the only **pan-European stakeholder network on antimicrobial resistance led by civil society**. It includes more than 80 leading organizations and individuals committed to tackling antimicrobial resistance in the context of the One Health approach.

In parallel and **in collaboration with this work, promoting the mobility of professionals** would accelerate the application of the discussed practices, as well as improve the evolution of practices towards an optimization of prescription, waste management and environmental consideration.

### **Awareness**

#### **Proposal 14 : Display the antibiotic resistance logo on the broad spectrum antibiotics most at risk.**

Following a large-scale competition, **EU-JAMRAI** chose a symbol to fight antibiotic resistance, which was then widely shared on social networks.

**Printing this symbol on the packaging of broad-spectrum antibiotics,** and those **most at risk of developing resistance,** would allow patients to visualize antibiotic resistance. Patients already aware of antibiotic resistance through advice from their health professionals would have a visual reminder of what they have learned, before taking antibiotics, which would promote adherence to antibiotics.

## Education :

**Proposal 15 : Include the topic of pharmaceuticals in the environment in undergraduate and graduate education and training programs for pharmacy students in order to empower them and emphasize the importance of environmental safety;**

A course dedicated to this topic in the core curriculum of pharmacy studies would enable all future pharmacists to acquire the necessary skills. This training must be complete, regularly updated and must deal with the notions of environmental health as well as the practices allowing to protect the population facing these new problems, it could deal with :

- Proper use of medication and eco-prescription
- Pharmaceutical advice focused on prevention of exposure to endocrine disruptors, lead, and other chemical components
- Detection and referral of the patient exposed to aggravating environmental factors during pharmaceutical interviews and pharmaceutical follow-up
- Taking care of the patient as a whole: his or her health, habitat and territory.

Practical skills and follow-up should have a significant place in these courses. teaching. This training must be integrated into the initial curriculum of pharmacy students. Pharmacy. Some teaching tools already present in some faculties could be generalized, allowing students to be generalized allowing students to put their knowledge into practice.

**Proposal 16 : Raise awareness on good practices in antibiotic resistance courses in universities.**

Among the biggest obstacles to innovation and change are the evolution of customs and the modification of work habits. In order to remove this obstacle and to promote good practices among prescribing professionals in a sustainable way, it is necessary to **adapt health curricula to topical public health issues.**

Thus, it is essential that **Member States invest in the training of health students** in order to teach good practices in antibiotic therapy. Indeed, it is the generational renewal of practitioners that will be the greatest driver of change.

According to [Health Care Without Harm's survey](#) of medical students in years 4-6 across Europe, 90% are keen to receive additional training on antimicrobials and their prescribing during their studies, including: choosing the right dose and administration interval, planning the duration of antimicrobial treatment, and selecting the best antimicrobial for an infection,

considering that 68% said they did not have a course dedicated solely to antimicrobial resistance. However, 80% of the students surveyed had already been in contact with resistant patients.

The desire for more advanced training is shared with other health students, who it would also be interesting to question. Indeed, EPSA, the European Pharmaceutical Students' Association, is working on the revision of the Professional Qualifications Directive, and is asking students about their training needs, particularly with regard to antibiotic resistance.

Several training formats are illustrated in the report by Health Care Without Harm, which can help policy makers to better target the format that works for students, and to promote it more widely to member states.

**Proposal 17 : Create working groups within European universities bringing together health students and professionals from different countries, and reflecting on the means of responsible prescribing.**

The cultural mix in universities is only possible through the involvement of **ERASMUS +** and the **students' and professionals' participation**. The working group would act as a link between various researchers/experts and even institutions from one country to another. A multi-annual renewal would also be possible, in order to diversify the profiles, increase the multicultural potential and make practices evolve.

Finally, the sums invested in these exchanges would be a **real public investment**. Exchanges could take place according to several themes predetermined by the universities.

**Proposal 18 : Promote interprofessional courses allowing students to work on concrete approaches to fight AMR, common to all health students**

The implementation of those courses would have a double advantage. First of all, it would **give students the opportunity to work interprofessionally on a major public health issue**. It would also give them the opportunity to **work in collaboration with specialists and researchers**, and to contribute to the development of strategies to combat antibiotic resistance.

This course could take several forms, depending on the availability of professionals within the faculty or campus. Several topics could be addressed, such as **prescription-dispensing issues, research and innovation, One Health issues in antibiotic prescription, waste management and environmental health**, etc. In addition to medical and pharmacy students, the course could be open to all health students who will be confronted with antibiotic prescribing during their professional career. For example, dental students or midwifery students will be required to prescribe antibiotics for their patients. Educating them alongside

medical and pharmacy students will only have a positive effect. Indeed, they will all have the same knowledge about antibiotic resistance and will be able to collaborate during the management of patients to fight against it.

### Surveillance of pharmaceuticals in the environment

#### Proposal 19 : Database with all APIs of medicinal substances, in order to allow a better surveillance of water pollution by Member States

Today, several hundred active pharmaceutical ingredients (APIs) have been found in wastewater, surface water, groundwater, soil, air or biota at concentrations ranging from subng/L to more than µg/L.(1, 2) To date, several examples of APIs have convincingly demonstrated their effects on organisms in the environment.

**Pharmaceutical classes identified as being of environmental concern include, for example, steroid hormones, antibiotics, analgesics, parasiticides and anxiolytic drugs.**

However, a **lack of transparency on the part of industry to public authorities limits the development of environmental analysis tools**, and therefore the collection of data. Moreover, **digital technology and artificial intelligence are tools that have proven their effectiveness in optimizing responsible prescribing**. Thus, collaboration between industries and national and European health authorities is necessary to facilitate the circulation of information and improve the monitoring of these products in the environment. Also, **a centralization by the European agencies is essential to allow access to these data to all transnational stakeholders**, and to allow a transposition of the **good practices specific to each Member State**. Through the elaboration of a list of critical products, and the multiplication of data on APIs, a better monitoring of our environment as well as the development of efficient tools will be possible on a large scale.

### Investing in innovations :

***Declining private investment and lack of innovation in the development of new antibiotics are limiting factors in the fight against the spread of resistance.** Despite the development of 50 antibiotics and 10 biodrugs worldwide, these have little benefit and do not specifically target the most resistant bacteria<sup>50</sup>. Other more innovative drugs are still in the pre-clinical stage, and will therefore have to wait several years before being marketed. One of the causes has been identified : it is mainly small and medium-sized companies that are involved in the research of new antibiotics.*

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<sup>50</sup> Le manque de nouveaux antibiotiques met en péril les efforts mondiaux visant à lutter contre les infections résistantes.  
<https://www.who.int/fr/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections>.

However, the market for antibiotics is currently too unprofitable for the pharmaceutical industry<sup>51</sup>. As previously mentioned, currently only small and medium-sized companies are interested in researching new antibiotics. However, if the research and development is not profitable before the molecule falls into the public domain, the enterprise risks bankruptcy. This is not an encouraging environment for new research. Also, to avoid the overuse of these antibiotics and therefore the development of resistance, it is recommended to deploy new products progressively and to limit their use.

### **Proposal 20 : Finance biotechnology research and development in small and medium enterprises, to avoid bankruptcy and to create a competitive market**

Small and medium-sized enterprises are a pillar of the EU economy, accounting for more than **99% of European businesses** and 2/3 of private sector jobs.

Improving the competitiveness of SMEs is one of the 11 thematic objectives of the [2014-2020 cohesion policy](#), and they are supported under other thematic objectives such as research and innovation. With an envelope of more than **65 billion euros**, which represents a financing of about 20% of the European Regional Development Fund (ERDF) explicitly dedicated to SMEs, the ERDF is one of the main providers of aid for the new strategy for SMEs, aimed at promoting "an economy that serves people". The increased use of financial instruments that mobilize additional European, national and regional funds in the 2014-2020 funding period also benefits SMEs.

The European Court of Auditors launched a [new audit in October 2020](#) to **assess whether EU funding for SMEs is helping to make the economy more competitive**. The auditors are examining whether the European Commission's ERDF support is helping start-ups and expanding companies to achieve sustainable gains in competitiveness. They will also making sure Member States are directing this funding to the right recipients, whether it meets the most relevant needs and whether the projects funded are producing results.

Thus, following the publication of this review, a review and renewal of funding would be necessary, as was the case following the results of the EU cohesion policy during the 2007-2013 funding period. It is essential to focus on funding for SME research and development, given the urgency of the need for innovation in antibiotic resistance and the time needed to bring a new active molecule to market, which is approximately 10 years.

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<sup>51</sup>Deluzarche, C. Indispensables mais en faillite: le paradoxe des antibiotiques. *korii*. <https://korii.slate.fr/biz/industrie-pharmaceutique-paradoxe-antibiotique-laboratoires-financement-fail-lite-rentabilite> (2021).

**Proposal 21 : Study of an economic model adapted to the antibiotic market to compensate for the delay in use and the low remuneration associated with short-term treatment, such as a remunerative price based on the costs avoided thanks to the treatment**

The current economic market is not conducive to the development of new antibiotics. Pharmaceutical companies' revenues are **dependent on sales volume**, which can be detrimental to antimicrobial stewardship initiatives, which take more than a decade to develop and cost approximately \$1 billion. Also, best practices recommend **reducing antibiotic prescribing**, which does not help offset the development costs.

In June 2020, the UK<sup>52</sup> announced that it would test innovative models that pay companies for antimicrobials based primarily on an **assessment of health technologies and their overall value to the NHS**, as opposed to volumes used. The principle is threefold : the government is offering contracts to develop new antibiotics to treat the deadliest diseases, NHS patients could benefit from new antibiotic treatments as early as 2022, and the new drugs will be paid for under the world's first subscription-based payment model for antibiotics.

The NHS is proposing two contracts to pay pharmaceutical companies up front for their work for access to innovative antibiotics, incentivizing them to bring new classes of drugs to classes of drugs to patients across the UK for the first time in nearly 30 years.

The results of the economic analysis will, where possible, expressed as net population health benefits, and measured in quality-adjusted life years. The net population health benefit should be estimated over time horizon of the economic model and the options presented to allocate an appropriate proportion of the total value to a potential contract period of ten years<sup>53</sup>.

This project will focus on two antibiotic molecules. Of particular interest are antibiotics that can **provide alternative treatment options for serious infections**, such as bloodstream infections, sepsis, and nosocomial pneumonia.

- An existing antimicrobial, ceftazidime with avibactam (manufactured by Pfizer).
- A new-to-market antimicrobial, cefiderocol (manufactured by Shionogi).

A scoping process has been initiated to define the specific focus of the project. This includes the clinical areas of greatest interest to the NHS and what will be included in the

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<sup>52</sup>World-first scheme underway to tackle AMR and protect UK patients. *GOV.UK* <https://www.gov.uk/government/news/world-first-scheme-underway-to-tackle-amr-and-protect-uk-patients>

<sup>53</sup>Cefiderocol for treating severe aerobic Gram-negative bacterial infections | Models for the evaluation and purchase of antimicrobials | Scientific advice | Life sciences | What we do | About. *NICE* <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/cefiderocol>.

economic analyses. The scoping projects and draft lists of stakeholder lists are currently out for consultation. Depending on the results of this study, it could be **scaled up to be studied in different health systems and advocated for countries with a similar model.**

### **Proposal 22 : Re-launch the DRIVE-AB initiative, especially WP2: Creation and testing of new business models.**

**DRIVE-AB<sup>54</sup>** is a public-private consortium funded by the **European Innovative Medicines Initiative (IMI)** and composed of 16 public and 7 private partners from 12 countries. This 3-year project started in October 2014. During these 3 years, the project conducted research with stakeholders, and disseminated their results at the end in 2017.

Its action areas were multiple:

- 1. Define standards and metrics for responsible antibiotic use.**
- 2. Estimating the current and future impact of antibiotic resistance** on societies to determine future public health needs
- 3. Quantify the value of new antibiotics**
- 4. Create, test and validate new business models** to encourage the discovery and development of discovery and development of new antibiotics
- 5. Recommend to governments and policymakers new business models** that stimulate innovation, responsible use, and global access to new antibiotics to meet public health needs

The action areas on good antibiotic practice (1, 2, 3) are currently being worked on by other EU stakeholder groups, including the **AMR Stakeholder Network, and EU JAMRAI**. However, the areas of action concerning the **economic value of innovation and research**, and the **testing of new business models**, have been neglected. Thus, re-launching this initiative within a working group is necessary, given the importance of the phenomenon and the need for a revision of the economic model to boost innovation.

### **Proposal 23 : Patent extension or market exclusivity for promising products in order to make their commercialization profitable and avoid them falling too quickly into the generic field.**

This lack of profitability frightens the most important pharmaceutical industries, and the development of these molecules is often left to SMEs, which sometimes have fewer means and resources.

To counter this phenomenon, **compensatory measures can be thought of**, in order to make this market more attractive, and at the same time more competitive. For example, **proposing**

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<sup>54</sup><http://drive-ab.eu/>

**a patent extension** would make it possible to ensure that there is a return on investment in the development of the molecule, despite a recommendation not to prescribe innovative molecules in large quantities.

In addition, it would also be possible to imagine a **re-evaluation of the patent at the time of the centralized MA application by the EMA**, in cooperation with the European Patent Office (EPO). Indeed, the possibility of filing a 10-year patent during the research and development stage will always be relevant, in order to secure the market during the development of the compound. However, with total transparency of the development costs and processes, a re-evaluation could be made and the patent could be re-evaluated in order to work on the profitability of the drug. This re-evaluation could be done only upwards, in order not to penalize the industries.

Several advantages to this process can be highlighted: **making R&D profitable, stimulating the antibiotic market, and promoting transparency in public-private collaboration.**

**Proposal 24 : Support actions such as the Antimicrobial Resistance Action Fund<sup>55</sup> through financial participation and acceleration of the marketing process.**

The **Antibiotic Resistance Action Fund** is an initiative of more than 20 leading pharmaceutical companies. These companies have committed to invest nearly \$1 billion with the goal of bringing two to four new antibiotics to market by 2030 and providing industry expertise to support the clinical development of new antibiotics.

In addition to strengthening and accelerating antibiotic research and development through investment and the provision of resources and industry expertise to biotech companies, it aims to bring together a broad alliance of industry and non-industry players, including philanthropic organizations, development banks and multilateral organizations, to encourage governments to create market conditions that allow for sustainable investment in the sector.

Thus, in order to revive the European market and encourage the relocation of industries in Europe, it seems essential that European agencies take part in this project, also to support SMEs in terms of regulatory science.

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<sup>55</sup> <https://www.amractionfund.com/>