

Special Report

Addressing antimicrobial resistance: progress in the animal sector, but this health threat remains a challenge for the EU



EUROPEAN
COURT
OF AUDITORS

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Executive summary

I Antimicrobial resistance (AMR) - when microbes develop resistance against medicines that were previously able to fight them - is a growing threat to global health. The European Centre for Disease Prevention and Control reported that it already leads to 33 000 deaths each year in the EU/EEA, mostly due to infections in hospitals and other healthcare settings. The World Health Organisation's "One Health" principle, which considers human health, animal health and the environment, recognises that an integrated approach to antimicrobials is needed.

II Fighting against antimicrobial resistance is complicated. It is challenging to apply good infection prevention and control measures in practice (including practices as basic as hand washing). It is also challenging to use existing antimicrobials prudently (both to treat humans and animals), meaning using the right drug correctly and only when needed. Finally, no new classes of antibiotics have been discovered for many years.

III In the EU, human health is a Member State competence. Article 6 and 168 of the Treaty on the Functioning of the European Union give the Union a mandate to support, coordinate, supplement and encourage cooperation between Member States for the protection and improvement of human health. Antimicrobial resistance is recognised by EU law as a serious cross-border threat to health, where EU action is required. Furthermore, there is clear Commission competence to act in veterinary issues, food safety, and research: all of which are relevant for antimicrobial resistance.

IV Our audit considered the rising threat of antimicrobial resistance and recent EU policy initiatives. We examined how the Commission and the European Centre for Disease Prevention and Control (ECDC) managed resources aimed at supporting Member States One Health approach to antimicrobial resistance, and whether the framework to improve the prudent use of veterinary antimicrobials and monitor antimicrobial resistance in food was being well applied. We also examined how the Commission supported AMR related research.

V We conclude that the activities of the Commission and agencies have led to some progress, for example, in veterinary and food related issues. However, there is little evidence to date that the health burden of AMR has been reduced in the European Union.

VI The Commission and ECDC support to strengthen Member States One Health approach to AMR was valuable, but had resulted in little demonstrable progress in reducing AMR. The Joint Action on antimicrobial resistance, to support national One Health policies, facilitated cooperation between Member States but faced challenges to the sustainable implementation of its results. A recent Commission funded study led by the OECD was a compass for cost effective options for Member States to reduce antimicrobial resistance in hospitals and other healthcare settings. Outcome indicators were not consistently used by the Member States we visited, or by the Commission, to monitor progress; data on health care associated infections, which are the primary source of AMR infections, was incomplete; and, at the time of our audit, there was insufficient knowledge about AMR in the environment.

VII The prudent use of veterinary antimicrobials is generally improving in the Member States. Between 2011 and 2016, sales of veterinary antimicrobials reduced by 20 %. However, there are big differences between the Member States, and consumption of some antimicrobials is still too high. Recent EU legislation on medicinal products and feed addressed some known weaknesses. The future Common Agricultural Policy provides an opportunity to further strengthen the EU framework for dealing with AMR.

VIII The antimicrobials market lacks commercial incentives to develop new treatments. Funding from the EU budget is a major source of investment for research, and has created structures to speed up the development of new antimicrobials. But EU funded public – private research initiatives experienced delays, and there have been no breakthroughs yet. The Commission has not comprehensively evaluated its approach to antimicrobial research, and its action plan does not address some of the specific challenges facing AMR research. Concrete initiatives to address market failures affecting provision of new antimicrobials are largely absent.

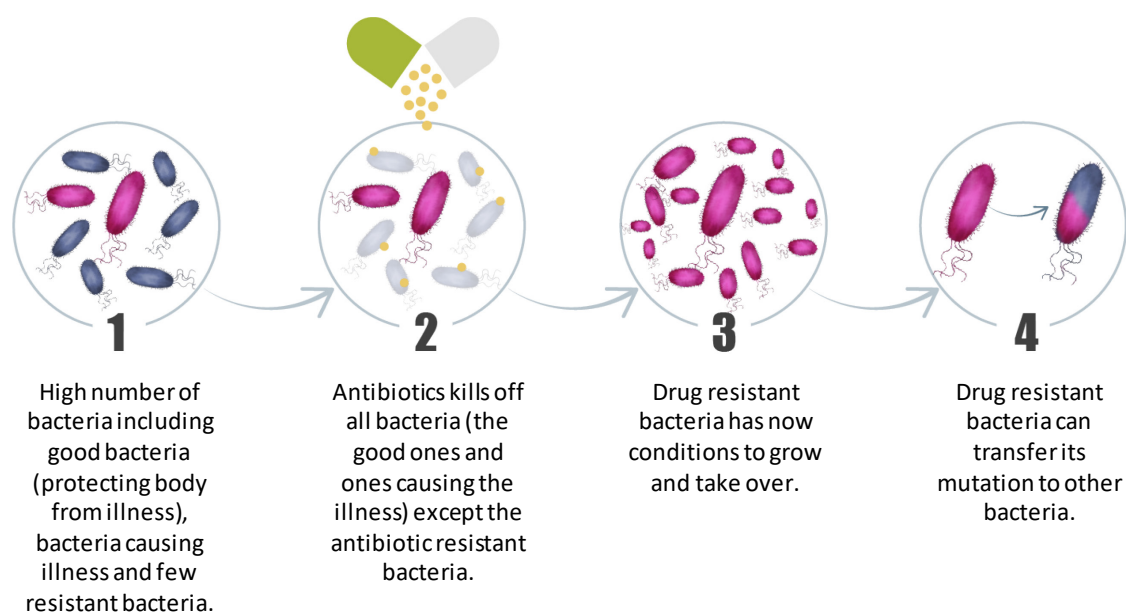
IX Based on our conclusions, we make recommendations aimed at strengthening the Commission's response to antimicrobial resistance through better support to Member States; promoting the prudent use of antimicrobials and better monitoring of antimicrobial resistance; and strengthening strategies for research.

Introduction

What is Antimicrobial Resistance

01 Antimicrobials are used to treat people, animals and plants. Antimicrobial resistance (AMR) happens when microbes (bacteria, viruses, parasites, and fungi) develop resistance against medicines that were previously able to fight them, making the treatment less efficient or completely ineffective. AMR develops naturally over time, usually through genetic changes¹, but it accelerates when antimicrobials are overused or misused i.e. are not used prudently – meaning the right drug is used when needed, at the right dose, frequency, and duration (*Figure 1* shows how AMR develops).

Figure 1 – How antimicrobial resistance develops



Source: ECA based on [United States Centers for Disease Control and Prevention \(CDC\)](#).

02 The World Health Organisation (WHO) identified AMR as a serious threat to global health, development and food security². The European Centre for Disease Prevention and Control (ECDC) reported³ that 33 000 people die each year, based on

¹ [Antimicrobial resistance – Key facts](#), WHO, February 2018.

² WHO (2017), [Antibiotic Resistance Fact Sheet](#), World Health Organization.

³ [Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015](#), the Lancet, 2018.

2015 data, in the EU / European Economic Area (EEA) from infections caused by drug resistant bacteria. AMR generates additional yearly costs of €1.5 billion⁴ due to extra healthcare costs and productivity losses. Infections caused by organisms that have developed resistance, usually acquired in hospitals and other healthcare settings, may require lengthier and costlier treatments, some with serious side effects (e.g. renal failure), and carry a higher risk of death for patients.

03 Nearly 40 % of the health burden of AMR is caused by bacteria resistant to last-line antibiotics (such as carbapenems and colistin). When last-line antibiotics are no longer effective, it is difficult and may be impossible to treat infected patients⁵.

04 In the EU / EEA, about two thirds of total antimicrobial use is for food producing animals⁶. Some of these then end up in the environment⁷. There is evidence that reductions in the use of antimicrobials in food-producing animals lead to reductions in the presence of antimicrobial-resistant microorganisms in these animals⁸.

05 Antimicrobials used to treat diseases that can be transmitted between animals and humans, such as campylobacteriosis and salmonellosis, are becoming less effective. Resistance to certain antimicrobials varies between different countries and type of microorganisms.

⁴ [EU Action on Antimicrobial Resistance](#), European Commission, 2017.

⁵ [ECDC infographic on AMR](#), November 2018.

⁶ See Table 5 of the most recent [JIACRA report](#) (from 2017) on the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food producing animals.

⁷ See, for example [WHO guidelines on use of medically important antimicrobials in food-producing animals](#) and [How do we reduce antibiotic resistance from livestock?](#), Hannah Ritchie, Our World in Data, November 2017.

⁸ See, for example, [“Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis”](#), The Lancet, November 2017; or [“WHO calls on food industry to stop routinely using antibiotics in healthy animals”](#), The Pharmaceutical Journal, November 2017.

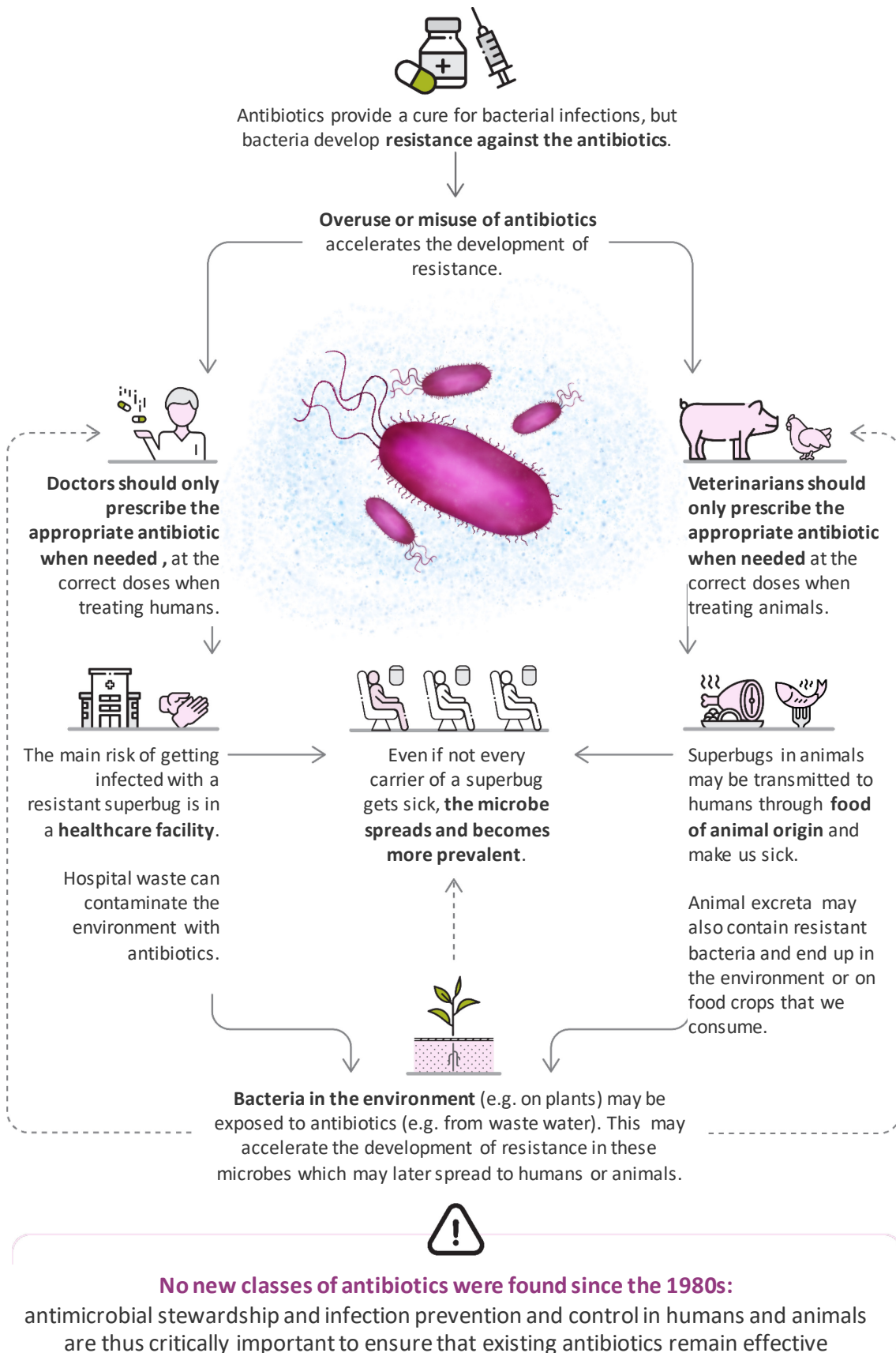
Why fighting AMR is complicated

06 The continued overuse or misuse of antimicrobials in the human and animal health sectors accelerates the development of antimicrobial resistance. The ECDC has reported some reductions in the consumption of antimicrobials for human health, with significant variations between Member States⁹. The prevention and control of cross-transmission of antimicrobial-resistant microorganisms in healthcare settings, in particular hospitals and long-term care facilities, is important. However, it is a challenge to ensure good infection prevention and control measures (such as hand hygiene, contact precautions, patient isolation, and cleaning) in practice. These measures require training, resources, and supervision across healthcare facilities; and need to be applied rigorously by the hundreds of thousands of healthcare personnel in the EU. In addition, ECDC data indicates that basic diagnostic tests in hospitals, required to target medical treatments, are not being carried out across the EU as often as necessary. This also contributes to the excessive use of broad-spectrum antibiotics.

Figure 2 illustrates how AMR can spread.

⁹ “Antimicrobial consumption – Annual epidemiological Report for 2017”, ECDC, 2018.

Figure 2 – How resistance to antibiotics spreads

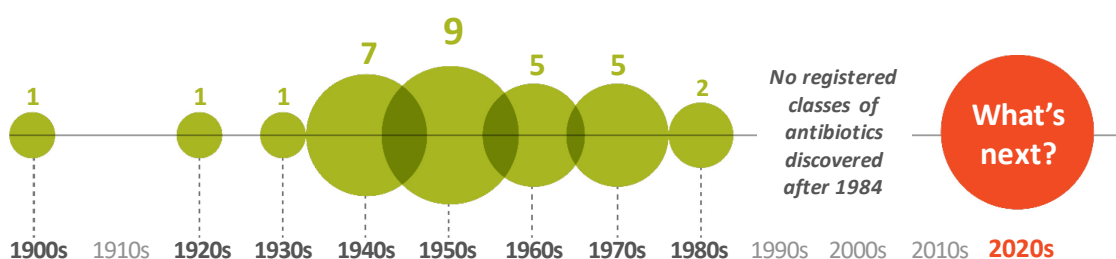


07 No new class of antibiotics has become available since the 1980s (see [Figure 3](#)). This absence of new drugs is complicated by the fact that some existing antibiotics, which continue to work, are no longer widely marketed by drug manufacturers. Several large corporations announced in recent years their withdrawal from antibiotics research and development¹⁰. Such research is a lengthy, uncertain and expensive process, and by definition any new drugs discovered will need to be used prudently to maintain their effectiveness. A recent project funded by the Joint Undertaking Innovative Medicines Initiative (JU IMI)¹¹ estimated that it could cost €1 billion to bring a new drug to the market.

Figure 3 – Discovery of new antibiotics

More than 30-Year Void in Discovery of New Types of Antibiotics

(Number of antibiotic classes discovered or patented)



Source: ECA based on “A sustained and robust pipeline of new antibacterial drugs and therapies is critical to preserve public health”, Pew Charitable Trusts, May 2016.

08 Ultimately the fight against AMR consists of two main challenges:

- o ensuring a more prudent and efficient use of existing antimicrobials (including by increasing awareness, better hygiene practices, training, surveillance and monitoring, and enhanced diagnostics) in humans, plants and animals;
- o and discovering and making available new antimicrobials (through research and development).

¹⁰ See, for example, [article](#) in “Chemistry World” from July 2018 and the 2018 OECD report “Stemming the superbug tide – Just a few dollars more”.

¹¹ DRIVE AB report “Revitalising the antibiotic pipeline”, 2018, from the New Drugs for Bad Bugs programme, 2018.

Global actions to fight antimicrobial resistance

09 The WHO Global Action Plan¹², adopted in 2015, required WHO member countries to develop and start implementing their National One Health Action Plan (NAP) by mid-2017. The WHO's "One Health" principle recognises that an integrated approach to antimicrobials is needed, which considers human health, animal health and the environment (see [Figure 2](#)).

10 The WHO's Global Database for AMR shows that Member States were at different stages in terms of developing and implementing NAPs¹³. According to a survey we conducted for our audit, out of 24 EU Member States that replied, 16 indicated having a NAP, five indicated having elements of one, and three indicated they did not have one.

11 The WHO Global Action Plan is mirrored by international efforts to cooperate on research for AMR. Since 2009, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) collaborates and shares best practices between North America and Europe. And in 2018, the G20 launched its Global Antimicrobial Resistance Research and Development Hub.

EU actions to fight antimicrobial resistance

12 Human health is a national competence. Articles 6 and 168 of the Treaty on the Functioning of the European Union (TFEU) give the Union competence to carry out actions to support, coordinate, supplement and encourage cooperation between Member States, for the protection and improvement of human health.

13 Decision 1082/2013¹⁴ of the European Parliament and the Council defines AMR and healthcare associated infections as serious cross-border threats to health, where action at Union level is needed. The Decision requires Member States to perform

¹² [Global action plan on antimicrobial resistance](#), WHO, May 2015.

¹³ [Global Database for Antimicrobial Resistance Country Self Assessment](#), from the WHO, World Organisation for Animal Health, and Food and Agricultural Organisation of the United Nations.

¹⁴ [Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC](#)

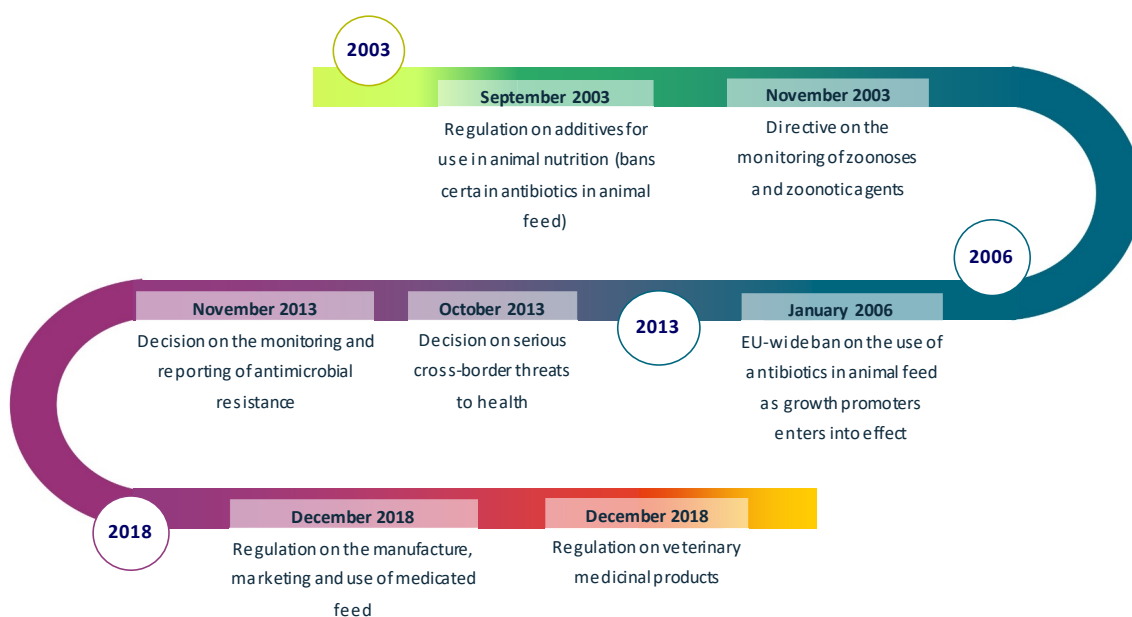
surveillance of AMR and healthcare associated infections (HAIs), and to report such threats via an Early Warning and Response System.

14 In contrast to the limited EU mandate for human health, EU legislation requires Member States to monitor and report the presence of resistant zoonotic and commensal bacteria in certain food of animal origin. An EU-wide ban on the use of antimicrobials as growth promoters in animal feed entered into effect on January 1, 2006. This ban was reinforced under the new EU Regulation on veterinary medicinal products.

15 In response to calls for action from the Council, the Commission launched a first AMR action plan in 2011 covering both human and animal health. In 2017, following Council conclusions, and the WHO's Global Action Plan, the Commission adopted its "European One Health Action Plan against antimicrobial resistance (AMR)", which contains actions relating to human health, animal health and the environment. The EU Action Plan is supported by measures co-funded from the EU Health Programme, which aim to help Member States to strengthen their national One Health approach. In 2019¹⁵ the Council issued new conclusions on AMR. *Figure 4* summarises the EU regulatory actions addressing the threat of AMR.

¹⁵ Council conclusions on the next steps towards making the EU a best practice region in combatting antimicrobial resistance 2019/C 214/01, June 2019.

Figure 4 – Main EU regulatory actions addressing antimicrobial resistance



Source: ECA.

16 The Commission addresses AMR by:

- providing funding from the Health Programme for relevant studies and joint actions. The Joint Action on Antimicrobial Resistance (JAMRAI) is one of the Commission and Member State responses to the Council Conclusions of June 2016 related to AMR. The Commission has also funded relevant actions by the WHO and OECD to support Member States;
- proposing a legislative framework on veterinary medicinal products and medicated feed that includes measures to fight AMR;
- issuing guidelines on the prudent use of antimicrobials in veterinary medicinal products and in human health;
- providing training and facilitating exchanges of experiences;
- establishing an EU AMR One Health network composed of government experts from the human health, animal health, and environmental sectors, as well as relevant EU agencies (ECDC, EMA and EFSA). The roles of the EU agencies in AMR are summarised in [Box 1](#);
- supporting research.

Box 1

The role of EU agencies in AMR

AMR is one of the areas of competence of several EU agencies.

The European Centre for Disease Prevention and Control (**ECDC**) supports Member States in their AMR activities. It runs an AMR and Healthcare-Associated Infections (ARHAI) programme; and gathers information from Member States on AMR and antimicrobial consumption from three surveillance networks. The ECDC produces scientific advice, including guidance documents and rapid risk assessments, conducts joint country visits with the Commission as well as training courses, and promotes prudent use of antibiotics by coordinating the European Antibiotic Awareness Day.

The European Food Safety Authority (**EFSA**) monitors antimicrobial resistance in food and food-producing animals, and produces scientific reports on the subject.

The European Medicines Agency (**EMA**) gives scientific advice, promotes prudent use of antimicrobials, and monitors sale volumes of antibiotics for animal health and manages the voluntary European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project that collects this information. It also provides scientific opinions for the marketing authorisation of antimicrobial medicinal products.

The Consumer, Health, Agriculture and Food Executive Agency (**CHAFEA**) manages the EU funding for AMR under the Health Programmes - including funding for the Joint Action on AMR.

17 Over 99 % of funding from the EU budget for AMR related actions is directed at research. EU Funding of AMR related research since 2004 has exceeded €1.5 billion. One of the flagship initiatives is the New Drugs for Bad Bugs Programme (ND4BB) launched in 2012, funded from FP7 and managed by the JU IMI. This aims to forge a public private partnership for the discovery, development and market entry of new antimicrobial treatments. The Commission also funds actions to coordinate and set an AMR strategic research agenda, particularly through the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR).

Audit scope and approach

18 Given the rising threat of antimicrobial resistance, reflected in the WHO Global Action Plan and the Commission action plan, we examined whether the Commission and relevant EU agencies managed well key activities and resources to support Member States and EU funded research aimed at fighting antimicrobial resistance. This included work which can contribute to the new AMR monitoring framework and the better use of antimicrobials. This main objective is broken down into three sub-questions:

- (1) Have the Commission and the ECDC managed well key activities and resources to support the One Health response of Member States to AMR under the EU Action Plan?
- (2) Have the Commission and EU agencies contributed effectively towards promoting the prudent use of antimicrobials in animals and reducing antimicrobial resistance in the EU?
- (3) Have the Commission and EU agencies had appropriate mechanisms to coordinate and evaluate EU support to AMR research?

19 To answer these questions, we have:

- examined the implementation of relevant actions funded from the 2014-2020 Health Programme;
- examined how the EU framework for AMR monitoring in food-producing animals and food, and for antimicrobial consumption in animals was implemented since 2013;
- surveyed national AMR Action Plan coordinators in all Member States to obtain targeted information on their actions and their views on the support they received from the Commission and the ECDC;
- consulted national and other authorities in Sweden, the Netherlands, Spain and France responsible for five of the nine work packages under JAMRAI most relevant for our audit; and for certain research projects. We also visited WHO Europe and the OECD;
- examined the Commission and agencies' support to AMR research since FP7, with a focus on the ND4BB programme. This included examining how beneficiaries implemented funded actions.

Observations

Commission and ECDC support for Member States' One Health approach has not yet delivered demonstrable results in reducing AMR

20 The Commission and ECDC support Member States to establish and implement their National One Health Action Plans (NAPs) for AMR, which they agreed to under their WHO commitments. This support is in terms of expertise through technical guidance, joint visits and surveillance networks; and through financial support for actions from the EU Health Programme. We therefore examined whether this support was well managed and contributed to sustainable results in addressing AMR. We also assessed whether information collected by surveillance networks was complete and relevant.



Commission funded actions supported the fight against AMR but faced challenges

21 The Commission provided support through funding relevant activities from the Health Programme for the Joint Action on Antimicrobial Resistance (JAMRAI), the WHO and the OECD (see [Table 1](#)). It also organised the One Health Network, provided guidance and training.

22 We obtained views from a survey of Member State authorities responsible for National Action Plans. These replies showed a general high appreciation of the quality of the support and guidance provided by the Commission - and the ECDC. Two thirds of respondents considered that JAMRAI provided effective support; and that the training provided by the Commission on the One Health approach was beneficial. Three quarters of respondents considered the One Health Networks were useful. Their views on the Commission's guidance on the prudent use of antimicrobials, for human and animal use, were similarly positive.

Table 1 – Measures funded from the Health Programme to support AMR policies

Action	Budget (000 euro)	Summary description
Joint Action on Antimicrobial Resistance (JAMRAI)	4 200	JAMRAI ¹⁶ aims at fostering synergies between EU Member States by developing and implementing effective One Health policies and reducing Health care associated infections; It has 9 work packages and 19 Member States, and provides a platform for exchange of experiences and developing best practices.
WHO	600	This action supports Member States to develop and implement national One Health action plans.
OECD	340	OECD assessed the economic burden of AMR. It calculated that actions to reduce AMR were good investments that would soon more than pay for themselves.

Source: ECA.

¹⁶ See [EU JAMRAI vision / mission](#).

The Commission-funded Joint Action on Antimicrobial Resistance (JAMRAI) faced challenges while facilitating cooperation between Member States

23 JAMRAI started on 1 September 2017, and will run for 36 months. We found that most JAMRAI work packages¹⁷ were generally on track to produce their agreed deliverables and that JAMRAI provides a good platform for exchanges of experiences and best practices between the 19 participating Member States¹⁸.

24 However, JAMRAI faced some challenges. It did not have a complete One Health approach, as there were no environmental authorities involved in Work Packages, and there was a relatively low participation from Member State veterinary authorities. Work Packages 4 (for integration in national policies and sustainability) and 7 (for the appropriate use of antimicrobials in humans and animals) were experiencing delays. Furthermore, JAMRAI's overall success will depend largely on actions subsequently taken by the Member States to actually implement the solutions developed by the work packages.

The WHO project had not supported the targeted numbers of Member States in its' first year of operation

25 The WHO project began in May 2018 and is scheduled to run for three years, to help Member States develop and implement national One Health action plans. The Commission arranged for WHO to present the project to Member States in the EU Health Security Committee in June 2018 and in the One Health Network. This project was behind schedule at the time of the audit and had not supported the targeted numbers of Member States for its various sub-objectives (a total of four instead of 8-12 for each sub-objective).

The Commission funded OECD study on the economic and healthcare burden of AMR was a signpost for targeted and cost-effective action

26 The OECD's report¹⁹ from 2018 concluded that tackling AMR was a good investment because there was a return in terms of avoided deaths and cost savings for

¹⁷ The nine work packages are: 1. Coordination; 2. Dissemination; 3. Evaluation; 4. Integration in national policies and sustainability; 5. Implementation of one health national strategies and national actions plans for AMR; 6. Prevention of healthcare associated infections; 7. Appropriate use of antimicrobials in humans and animals; 8. Awareness raising and communication; and 9. Prioritizing and implementing research.

¹⁸ Plus Norway.

¹⁹ "Stemming the superbug tide - Just a few dollars more", OECD, 2018.

healthcare systems. It showed that actions to reduce AMR were relatively cheap, cost-effective and feasible (see [Box 2](#)).

Box 2

OECD report findings - an invitation for action

The 2018 OECD report “Stemming the superbug tide – Just a few dollars more” indicates that three out of four deaths from superbug infections could be averted by spending just \$ USD 2 per person a year on measures as simple as facilitating handwashing and more prudent prescription of antibiotics.

Up to 1.6 million lives would be saved by 2050 across the 33 countries included in the OECD analysis, by using measures such as: promoting hospital hygiene; reducing over-prescription of antibiotics; improving antimicrobial stewardship programmes; mass media campaigns; and the use of rapid tests to detect whether an infection is bacterial or viral.

OECD considers that investments in these measures could pay for themselves within one year and produce savings of about \$ 1.5 USD for every dollar invested afterwards. Combining these measures in a coherent way would yield even higher benefits and savings.

27 In this context we note that health is not a strategic investment priority for the Structural Funds in the current programming period, but that the Structural Funds are used for the investments in health. A Commission-funded study²⁰ found that 7 404 health projects were funded by the Structural Funds between 2014-2018, with a total allocation of €8 billion. Only two of these projects were identified as having specific AMR objectives. The study identified that the intended inclusion of the EU Health Programme in the Structural Funds under ESF+ was an opportunity to achieve further synergies between funding instruments and investments in cross-sectoral collaboration²¹.

²⁰ ESI Funds for Health – [Investing for a healthy and inclusive EU](#) – Final Report, Milieu Law and Policy Consulting, 2019.

²¹ Also see “[Health sector study EU – Final Report](#)” prepared by EY and Technopolis under a Framework Agreement to support EIB Advisory Services, March 2019.

ECDC actions provided valuable support to the Commission and Member States in fighting AMR

28 The ECDC performs a range of AMR related tasks. It coordinates surveillance of AMR, antimicrobial consumption and healthcare-associated infections with three networks, i.e. the European Antimicrobial Resistance Surveillance Network (EARS-Net); the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) and the Healthcare-Associated Infections surveillance Network (HAI-Net), under the AMR and Healthcare-Associated Infections (ARHAI) programme. These surveillance networks provide key scientific information in a harmonised format, which is used for ECDC's scientific advice, training, country visits and awareness raising activities. The ECDC uses information from these networks to contribute data, on behalf of EU / EEA countries to the WHO.

29 ECDC performs country visits aimed at providing assistance to national authorities. Between 2006 and 2017, ECDC conducted 25 such visits devoted to the use of antimicrobial agents in human medicine. Since the launch of the EU One Health Action Plan in 2017, ECDC and the Commission perform joint country visits in a One Health approach, combining human and animal health. These are performed upon invitation from a Member State. By April 2019 there had been six such visits (compared with an initial plan to do six per year), as most Member State have not requested them. The replies to our survey indicated that these visits had a significant impact on the development of AMR actions by the Member States concerned.

30 We noted that ECDC received an increasing number of AMR-related requests for assistance. It postponed activities when more important requests took priority. We consider that ECDC's activities inform both the Commission and Member States, while noting the increasing risk that ECDC cannot perform important AMR work on time.

There were gaps in information on outcomes and surveillance of AMR

31 The Commission's overall objective is to make the EU a best practice region for AMR and antimicrobial consumption. In the context of its EU action plan, it thus requested the EU agencies (ECDC, EFSA and EMA) to produce a scientific opinion on outcome indicators for AMR One Health Action that could use existing surveillance data. Those indicators should assist Member States in monitoring their progress in reducing the use of antimicrobials and AMR in humans and food-producing animals, and to set targets to decrease risks of AMR.

32 Following this request, the agencies produced a Joint Scientific Opinion on outcome indicators in October 2017²². At the time of the audit (April 2019), we found that the status of these outcome indicators was uncertain, and that they were not consistently used by the Member States we visited, or by the Commission, to monitor progress.

Surveillance of healthcare associated infections was incomplete despite EU legal requirements

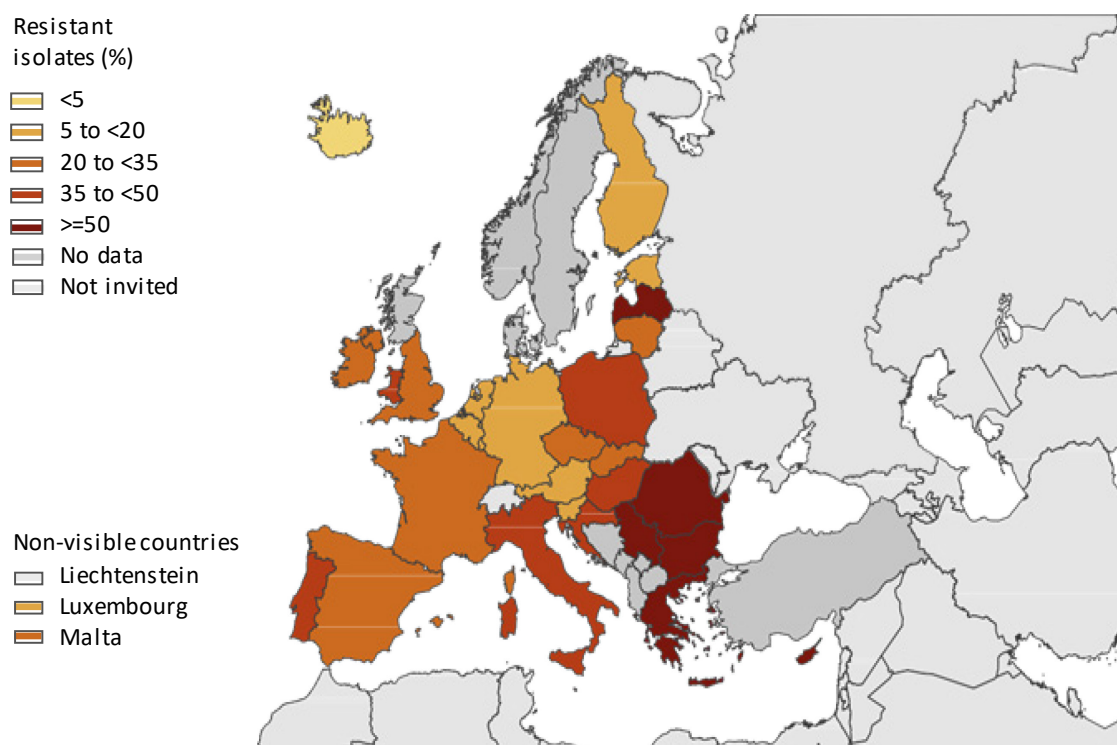
33 There is consistent evidence²³ that healthcare associated infections (HAIs) are the primary source of infection by AMR in humans in Europe. According to ECDC data, transmission of resistant bacteria in hospitals and other healthcare settings is a serious issue since almost nine million HAIs occur in the EU each year. This study showed that the contribution of various antibiotic-resistant bacteria to the overall burden varies greatly between countries. The ECDC has identified that in five Member States, more than half of healthcare associated infections in acute care hospitals were caused by resistant bacterial pathogens (see [Figure 5](#)).

²² ECDC, EFSA and EMA Joint Scientific Opinion on a list of outcome indicators as regards surveillance of antimicrobial resistance and antimicrobial consumption in humans and food-producing animals, October 2017.

²³ Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis, A. Cassini, *The Lancet*, January 2019.

Figure 5 – AMR in HAI from acute care hospital according to the data collected by the ECDC

In 2018, ECDC developed a composite index of AMR in Healthcare Associated Infections from acute care hospitals.



Source: ECDC, 2018; Adapted from: Suetens C, et al. *Euro Surveill.* 2018;23(46):pii=1800516.

34 In its Recommendation of 9 June 2009²⁴ the Council already recommended Member States to engage in prevalence surveys and surveillance of targeted infection types, using where appropriate ECDC recommended surveillance methods and indicators agreed at Community level. However, the surveillance of HAIs is a complex and resource intensive exercise, in particular because it relies on patient information that needs to be collected at the hospital level. It also requires extensive data validation.

35 We found that HAI surveillance data for the EU is incomplete. Involvement in ECDC surveillance²⁵ ranges from six Member States that participate in all five modules of ECDC's HAI-Net surveillance network to three Member States that participate in one

²⁴ Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections (2009/C 151/01).

²⁵ This surveillance was formalised following Council recommendations of 9 June 2009 on patient safety (2009/C 151/01).

module. The incompleteness of the surveillance data is likely to slow down actions against AMR.

36 The environment is one of the pillars of the One Health approach to AMR, together with human health and veterinary issues. We note that better addressing the role of the environment was a specific objective under the Commission’s current One Health Action Plan. There is little information targeting the process of transmission of AMR through the environment, when compared with human health and animal health sectors. The environmental sector is not specifically included in the JAMRAI Work Packages, nor under the various EU surveillance systems for AMR. In 2019 the Commission adopted a communication²⁶ on a “European Union strategic approach to pharmaceuticals and the environment”, which included the objective to identify actions to combat AMR. We also note that a scientific report²⁷ by EFSA from 2019 suggested the monitoring of AMR in the environment.

The prudent use of veterinary antimicrobials in the Member States has improved

37 The excessive use of veterinary antimicrobials, and AMR in animals and food, are vectors in the development of AMR in human health, and are areas where the EU has clear competences (see paragraph 14). We therefore examined whether there was evidence that veterinary antimicrobials were better used and whether the EU rules on the monitoring and reporting of AMR in zoonotic and commensal bacteria were applied well in practice. We also reviewed to what extent new EU rules for veterinary medicinal products and medicated feed address weaknesses.

²⁶ Communication from the Commission COM (2019) 128 of 11.03.2019 to the European Parliament, the Council and the European Economic and Social Committee: “European Union Strategic Approach to Pharmaceuticals in the Environment”.

²⁷ Technical specifications on harmonised monitoring of antimicrobial resistance in zoonotic and indicator bacteria from food-producing animals and food.



Some Member States have deployed successful strategies to reduce the use of antibiotics in veterinary medicine

38 The consumption of antimicrobials by food producing animals is much higher than in humans²⁸, whether in terms of total consumption, or in terms of doses compared with weight. European agencies have recognised that the reduction of the use of veterinary antimicrobials is a desirable objective to contain AMR. The European Medicines Agency has reported that sales of veterinary antimicrobials, in relation to total livestock (expressed as mg sold per Population Correction Unit (PCU))²⁹ dropped by 20 %³⁰ for the EU as a whole between 2011 and 2016; but also that there were large differences in sales and use of different classes of antimicrobials across the EU. In six Member States, sales of antimicrobials increased by more than 5 %. *Annex I* shows detailed sales per country. *Figure 6* shows that sales in the Member States of veterinary antimicrobial agents, expressed as mg sold per PCU³¹ varied widely.

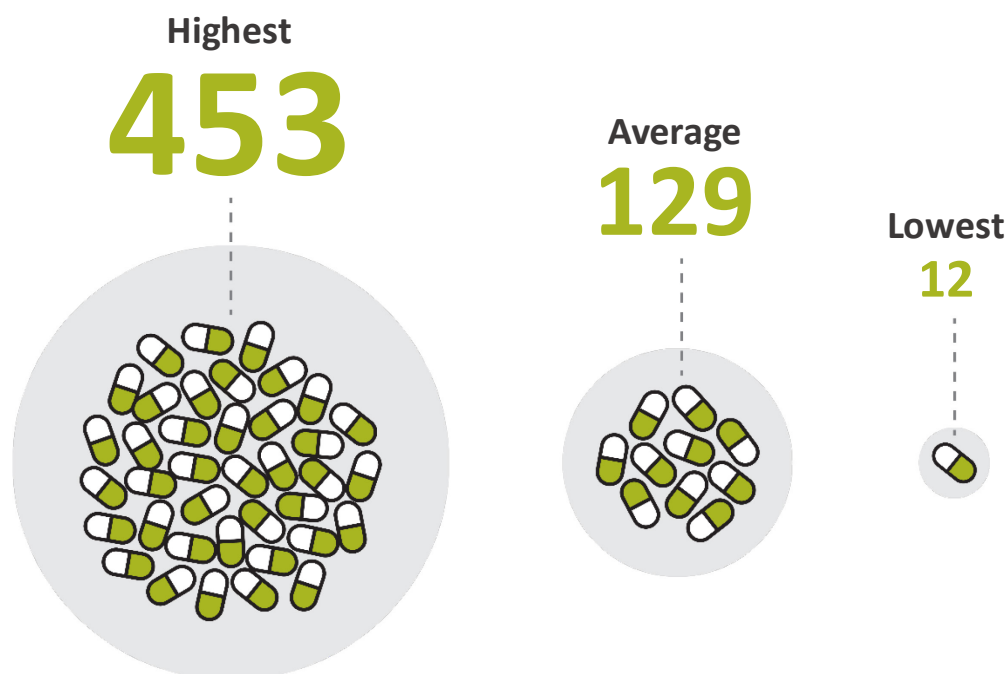
²⁸ See Table 5 of the most recent *JACRA report (from 2017)* on the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food producing animals.

²⁹ “Population Correction Units” are used to reflect the size of the animal population and weight of different species.

³⁰ European Medicines Agency, “Sales of veterinary antimicrobial agents in 30 European countries in 2016 – Trends from 2010 to 2016”, *Eighth ESVACS report*, London, 2018, p. 14.

³¹ See Table 4 *8th ESVAC report*.

Figure 6 – Sales of veterinary antimicrobial agents for food producing animals vary widely across Member States



Note: EMA advised in its recent ESVAC report not to use data to directly compare countries. 2016 sales as mg per Population Correction Unit.

Source: Adapted from Table 4 8th ESVAC report, EMA.

39 We visited the competent authorities in four Member States to discuss their experiences aimed at achieving a more prudent use of antimicrobials in veterinary medicine. **Box 3** shows some of the good practices they followed to achieve results.

Box 3

Member States can reduce the use of veterinary antimicrobials

Sweden has the lowest rate of consumption of veterinary antimicrobials in the EU. A focus on animal health, welfare and biosecurity at farms contributed to this. Infection prevention and control plans are mandatory for all farms, antimicrobials are used only on prescription, and national data on the use of veterinary antimicrobials has been collected for many years.

In the **Netherlands, France** and especially **Spain**, the historic use of veterinary antimicrobials was high. The use of veterinary antimicrobials in both France and the Netherlands approximately halved between 2011 and 2016. Although Spain achieved a reduction of 13 % between 2014 and 2016, it remained one of the Member States with a very high use of veterinary antimicrobials. While the situation is different in each of these countries, the actions taken included setting specific national reduction targets and plans; organising close cooperation between farmers, veterinarians and food producers; and restricting the use of last resort antibiotics in the veterinary sector.

A specific case: significant reduction in the use of colistin in Spain

Colistin is a last-resort antibiotic that should only be used under specific circumstances (see paragraph 03). In 2014, Spain had the highest veterinary use of colistin in the EU (using 37 mg / PCU). An action plan was launched and competent authorities worked with veterinarians and professionals representing the pig farming sector to agree on reducing the use of colistin. A quantitative target of 5 mg/PCU was set for a three-year period, while also putting in place controls to avoid increased use of alternative antibiotics. The use of colistin dropped to 7 mg/PCU by the start of 2018 (close to the EU average).

The new EU legal framework addressed some known weaknesses

40 The new EU Regulations on veterinary medicinal products³² and medicated feed³³ will strengthen the approach in fighting AMR (see **Box 4**), by requiring the more prudent use of antimicrobials by the Member States, and regulating the data collection

³² Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC.

³³ Regulation (EU) 2019/4 of the European Parliament and of the Council of 11 December 2018 on the manufacture, placing on the market and use of medicated feed, amending Regulation (EC) No 183/2005 of the European Parliament and of the Council and repealing Council Directive 90/167/EEC.

framework. The Commission plans to adopt implementing and delegated acts to complete the new EU framework in this area by early 2022.

Box 4

Main weaknesses for AMR addressed in new EU Regulations for veterinary medicinal products and medicated feed

The new regulations will in particular:

- ban the preventive use of antibiotics in groups of animals, and restrict the metaphylactic use of antimicrobials;
- reinforce an existing ban on using antimicrobials as growth promoters in feed;
- ban the preventive use of antimicrobials through medicated feed;
- introduce an option to reserve certain antimicrobials for human use only;
- require Member States to deliver detailed data on sales and use of antimicrobials that reflect consumption at farm level (in addition to the current voluntary system to collect data based on total sales);
- require third countries to comply with certain restrictions for their exports to the EU (respecting the ban on antimicrobials for promoting growth and increasing yield, and the restrictions on antimicrobials designated as reserved for human use in the EU).

41 However, we found that there are challenges ahead for the Commission and the Member States in rolling out this framework. In particular, the summary of product characteristics for the use of old medicines, including antimicrobials, need to be updated so they can continue to be used.

42 In addition, Member States will need to collect data on the sales and use of antimicrobials, to evaluate directly or indirectly the use of such products in food producing animals at farm level. During our visits to the Member States, we noted that collecting farm-level data was a major challenge. Some Member States may need support from the Commission to develop a data collection system to meet the new EU requirements. At the time of the audit, the Commission was exploring options for providing such support.

43 In the proposal for a future common agricultural policy (CAP)³⁴ the Commission indicated that its intention was to improve the response of EU agriculture to societal demands on food and health, including on antimicrobial resistance. The prevention of AMR will be part of the compulsory scope of the farm advisory services, and national authorities will be required to offer advice on the farm practices preventing the development of AMR as set out in the Commission's One Health Action Plan.

Monitoring of certain resistant bacteria in food and animals has improved, but gaps remain

44 The Member States we visited implemented the requirements contained in the relevant Commission Decision³⁵ on the monitoring and reporting of antimicrobial resistance. We noted that they performed additional surveillance going beyond the EU requirements. However, we also noted certain risk areas that merit consideration in the context of the planned revision of this Commission Decision, which we summarise in *Box 5*.

³⁴ Commission proposal establishing rules on support for strategic plans to be drawn up by Member States under the Common agricultural policy (CAP Strategic Plans) COM(2018) 392.

³⁵ 2013/652/EU: Commission Implementing Decision of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria.

Box 5

Risk areas for the future EU framework on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria

There are health risks related with AMR stemming from third country food imports, and in particular aquaculture products and fresh meat, but insufficient data is available to assess the seriousness of the risk and whether specific EU requirements for monitoring AMR in these products is needed. We note that similar issues were also addressed in a 2019 scientific report from EFSA³⁶.

The current EU monitoring and reporting requirements cover cattle, pigs and poultry for meat consumption which are the most commonly consumed species for the EU as a whole. In some parts of Europe species other than those covered by the 2013 Commission Decision such as ducks, rabbits, goats and sheep are also frequently consumed. Some countries may perform monitoring of AMR in food originating from these species but this is not required by the EU framework.

45 The Commission's right to inspect Member States' implementation of the AMR monitoring framework is one of the few firm pathways available to the Commission to check how Member States apply AMR veterinary related actions, and support their better implementation. Commission reports are publicly available³⁷. Between 2014 and 2018, the Commission examined 14 Member States, including three³⁸ of the four Member States we visited in the course of this audit. The visits had provided it with assurance that the Member States were meeting their veterinary related AMR monitoring obligations. We found that Commission work was of good quality and contributed to improvements in the national monitoring frameworks. The Commission suspended its visits at the end of 2018, as it considered that the primary objectives of the audit work had been met, and as it planned to revise the monitoring and reporting framework.

³⁶ [Technical specifications on harmonised monitoring of antimicrobial resistance in zoonotic and indicator bacteria from food-producing animals and food.](#)

³⁷ [The Commission's DG SANTE publishes its reports.](#)

³⁸ Spain, France, the Netherlands.

The EU budget provides significant support for AMR research but this has not yet resulted in major breakthroughs

46 The research and development of new antimicrobials, alternative treatments and vaccines is a highly complex and very important element in the fight against AMR. This is where the bulk of the EU's funding of AMR related actions is directed. We examined whether research efforts followed a strategic approach and addressed key challenges, while encouraging sustainable results.



The Commission coordinates AMR research efforts but has not comprehensively evaluated its approach

47 In its 2017 Action Plan the Commission reported that it had spent over €1.3 billion on AMR research since the start of the 2000-2006 programming period. In addition, JU IMI allocated €367 million to the New Drugs for Bad Bugs Programme (ND4BB). The EU budget finances at least as much on AMR research as all EU Member States combined. The Commission takes an active role in coordinating its R&D efforts internationally (e.g. G20 hub for AMR Research and Development, Transatlantic Taskforce on AMR, JPIAMR).

48 The majority of the Commission funded research effort was on the search to develop new antimicrobials, alternative treatments and vaccines. This funding uses grant payments, which help “push” ideas for new drugs through development phases (see [Figure 7](#) below) and ultimately to their commercialisation. This funding is exposed to high risks, because AMR research is inherently complex; the commercial industries

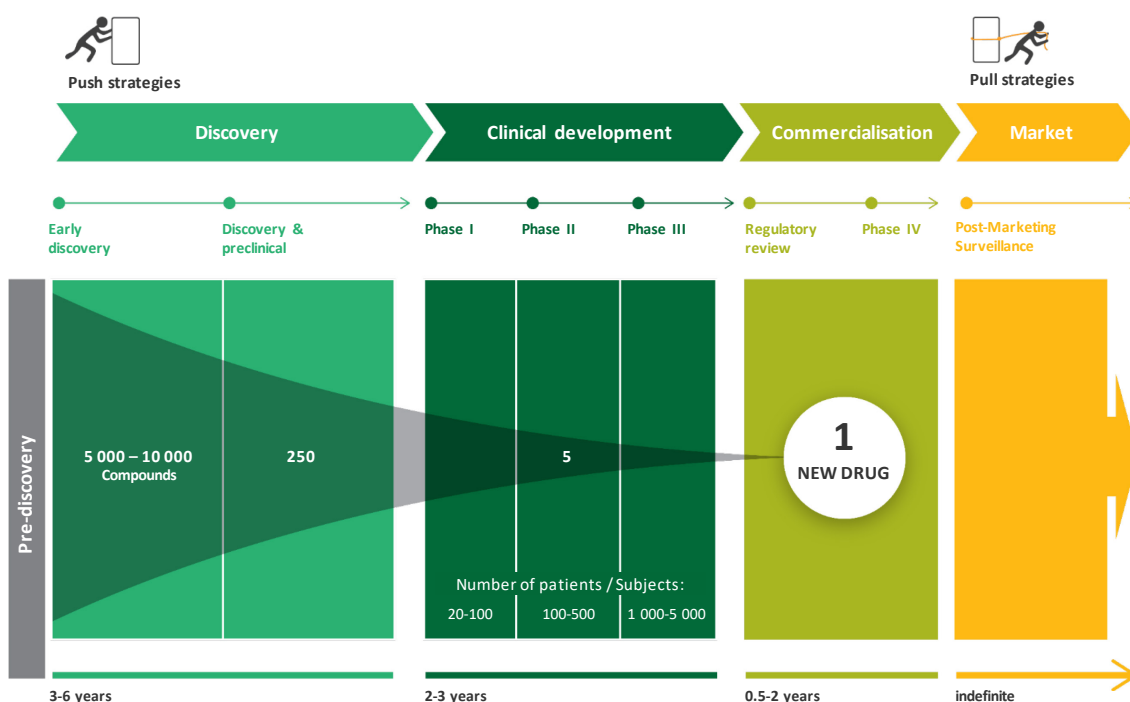
have largely lost their appetite to invest in this area (see paragraph 07); and there are currently no specific “pull” economic incentives (such as market entry rewards and long term supply continuity models). Indeed research efforts have so far not lead to new antimicrobials in many years (see [Figure 3](#)).

49 The Commission has not made a comprehensive evaluation of its support to AMR research, an activity that represents over 99 % of the EU budget for AMR. This is important when, as the recent OECD study shows (see [Box 2](#)) investments in improved hygiene, infection prevention and antimicrobial stewardship in healthcare are a cost-effective way to spend public money and effectively reduce the threat posed by AMR today. Furthermore, research into AMR in the environment has become important to provide robust evidence for further policy making.

EU funded research produced some positive results, while struggling to address some significant challenges

50 We focused our examination on the ND4BB programme – a ground breaking EU public private initiative to combat AMR by boosting the discovery and development of new treatments (see [Annex II](#)). The total value of the programme exceeds €650 million, which includes €367 million in EU budget funding. [Figure 7](#) shows the typical stages in the search for new antimicrobials.

Figure 7 – Stages in bringing new antimicrobials to market



Source: ECA adopted from COMBACTE managing entity (University Medical Centre Utrecht).

51 We noted that two of the seven projects comprising the ND4BB programme (Translocation and Drive-AB) were executed within the estimated timelines and budgets. One (ENABLE) is on track to meet or exceed its objectives within budget, while the remaining four projects (the Combacte and iABC projects) incurred significant delays in using available funds. As shown in [Table 2](#), more than half way through the lifecycle of the programme at the end of 2018, progress was significantly behind the initial planning and only a quarter of the budget for ND4BB was committed. The delays are not surprising in a field as volatile and complex as antibiotic drug discovery and development. It is extremely difficult to pursue this kind of activity within the constraints of a traditional project-driven and grant-funding approach.

Table 2 – Progress on the ND4BB programme is delayed

Project name	Total duration Months	Project START date	Project END date	% time elapsed to 31/12/2018	IMI total contribution (million euro)	Total Committed (budgeted) EFPIA in-kind (million euro)	Total IMI costs validated by 31/12/2018 (million euro)	% of IMI total paid by 31/12/2018	Total EFPIA in kind contribution validated by 31/12/2018 (million euro)	% of EFPIA total in-kind contributions validated by 31/12/2018
COMBACTE-NET	98	01/02/2013	28/02/2021	73 %	110	110	28	25 %	22	20 %
TRANSLOCATION	66	01/01/2013	30/06/2018	100 %	16	8	16	100 %	7	88 %
ENABLE	72	01/02/2014	31/01/2020	82 %	59	23	19	32 %	16	70 %
DRIVE-AB	39	01/10/2014	31/12/2017	100 %	6	3	6	100 %	2	67 %
Combacte-CARE	60	01/03/2015	29/02/2020	77 %	24	60	5	21 %	15	25 %
Combacte-MAGNET	84	01/01/2015	31/12/2021	57 %	75	92	13	17 %	11	12 %
iABC Programme	77	01/08/2015	31/12/2021	53 %	24	30	7	29 %	8	27 %
Sub total					314	326	94		81	
Other projects (mainly under Horizon 2020)					53	34	0		0	
Total ND4BB					367	360	94	26 %	81	23 %

Note: EFPIA: European Federation of Pharmaceutical Industries and Associations.

Source: ECA based on the information provided by Joint Undertaking Innovative Medicines Initiative (JU IMI).

52 The process from drug discovery to placing new treatments on the market is very complex and typically lasts up to 15 years (see [Figure 7](#)). ENABLE is a drug discovery platform for antibiotics targeting gram-negative bacteria, which are the most difficult to treat with antimicrobials. ENABLE funds investments in specialist expertise and networking (involving the private sector and academia) needed for drug discovery and pre-clinical development. Such technical expertise is particularly valuable for SMEs and academic organisations. This platform increases the chances to identify compounds that can quickly get through clinical development. Its aim was to lead to one product which could pass to clinical trials. At the time of our audit there were still five drugs in the ENABLE pipeline, from a starting point of over 100 expressions of interest, exceeding the initial target significantly. However, there is a risk that the efforts to develop the five drugs still in the pipeline will slow down if the platform ends as

scheduled in 2020, and that they will delay passing to clinical development - especially as three of these are owned by SMEs and one by an academic institution.

53 The Combacte/iABC projects last up to 7 years, and aimed to support the construction of critical infrastructure and networks to assist the faster discovery and clinical development of new antimicrobials. By the time of our audit, the projects had largely succeeded in creating this infrastructure, but there was no EU mechanism to finance the infrastructure after the projects' end.

54 The Combacte-NET and Magnet clinical development projects were trialling promising new products, and the construction of the network infrastructure has yielded valuable results. These projects facilitate capacity building for clinical trials and development in countries that face high levels of AMR. The projects are also attracting the interest of non-European companies in the field of antimicrobial development, and there was collaboration with a similar American research project. EU budget funding for these projects is scheduled to end in 2021.

55 The Commission awarded a grant in 2018 to the Managing Entity of the Combacte projects to develop a business model for a new clinical trials network (ECRAID - plan), to merge the existing "Combacte" network with a clinical trials network developed for emerging infectious diseases. ECRAID - plan is scheduled to start in 2021. At the time of our audit there was no agreed process to maintain the infrastructures developed under Combacte.

56 In the EU One Health Action Plan on AMR, the Commission set the objective to support SMEs in their research and development efforts. The role of SME's in the discovery of antimicrobials is increasing, particularly given the withdrawal of large pharmaceutical companies from such research (see paragraph **07**). Only about 5 % of funding from the ND4BB programme had been used for SMEs, mostly under the Enable project for drug discovery.

57 The EU One Health Action Plan provides a strategy for the Commission's support and research activities. It includes planned actions to improve knowledge on detection, infection control and surveillance; develop new therapeutics and alternatives; and develop new preventive vaccines. However the Action Plan does not address all of the specific challenges for AMR research, notably:

- the long timelines and challenges involved in the discovery and development of new antibiotics;

- how to integrate long term research priorities and sustain activities across programming periods;
- methods for working with all relevant stakeholders (academics, SMEs, pharmaceutical industries, international funding and coordination initiatives).

Commission initiatives have not yet resolved the market failures in antimicrobial research and development

58 Pharmaceutical companies have decided to withdraw from the market of certain Member States some antimicrobials that continue to work³⁹, such as a first-line treatment option for community-acquired pneumonia, and a recommended treatment for certain urinary tract infections. The Commission does not have an explicit mandate to propose initiatives to avoid or slow down the withdrawal of existing antimicrobials from the market.

59 In its 2017 EU One Health Action Plan on antimicrobial resistance, the Commission had tasked itself with supporting research into the development of new economic models to support the development of new antimicrobials.

60 We found that despite the general withdrawal of pharmaceutical industries from antimicrobial research, JU IMI together with its partners was overall able to maintain the expected level of public-private collaboration in the ND4BB programme (see [Table 2](#)). While this is encouraging, there are concerns about the insufficient commercial incentives for pharmaceutical companies to invest in this field.

61 The Drive-AB project produced a report in March 2018 making recommendations for strengthening the investment climate and pipeline for new antimicrobials. The report confirmed that the market for developing new antimicrobials was in general not commercially attractive. It explained how push incentives such as grants may pay for the costs of R&D but did not improve the attractiveness of the overall market. The report concluded that pull mechanisms were needed. It estimated that approximately €1 billion would be necessary for a market pull mechanism to successfully bring one first-of-a-kind new antibiotic to the market. The Commission has disseminated the results of the Drive-AB study to Member States, and in consultation with international partners (see paragraph [47](#)) was considering next steps to boost development of new

³⁹ See “[Tackling Drug-Resistant Infections Globally: Final report and recommendations](#)”, 2016, by the UK Review on AMR; [Unavailability of old antibiotics threatens effective treatments for common bacterial infections](#)”, *Lancet* Volume 18 2018.

antimicrobials. By the time of our audit the Commission had not decided on specific initiatives to promote pull mechanisms.

Conclusions and recommendations

62 Antimicrobial resistance (AMR) happens when microbes develop resistance against medicines that previously worked. It is a serious and growing threat to global and European health. An estimated 33 000 people already die each year in the EU / EEA from infections caused by drug resistant bacteria, leading to additional costs of €1.5 billion. The EU follows the “One Health” approach to AMR, with an integrated approach to human health, animal health and the environment.

63 Human health is a Member State competence. The Commission’s role is to complement and support Member States’ actions. There are EU rules on monitoring the consumption of antimicrobials and on the surveillance of resistant infections. The Commission’s mandate for action is more clearly defined for veterinary and food related issues (paragraphs [14](#) to [16](#)).

64 We examined whether the Commission and relevant EU agencies managed well key activities and resources to support Member States and EU funded research aimed at fighting AMR (paragraphs [18](#) and [19](#)).

65 We conclude that the activities of the Commission and agencies have led to some progress, for example, in veterinary and food related issues. However, there is little evidence to date that the health burden of AMR has been reduced in the European Union.

66 We found that the Commission and ECDC support to strengthen Member States’ One Health approach to AMR, while appreciated by the Member States and having the potential to provide a positive impact, has not yet delivered demonstrable results in reducing AMR. We found that the EU funded Joint Action on antimicrobial resistance (JAMRAI) facilitated cooperation between Member States but faced challenges, particularly to the sustainable implementation of its results in the Member States (paragraph [23](#) and [24](#)). An EU funded and OECD led project demonstrated that there was a range of relatively simple, cheap and cost effective options (antibiotic stewardship programmes, infection prevention and control measures, media campaigns and the use of rapid diagnostic tests) to reduce AMR in hospitals and other healthcare settings. We consider that further synergies are available to support the fight against AMR by targeted, cost-effective investments co-financed with EU support in those Member States that need to take more incisive action (paragraphs [26](#) and [27](#)).

67 We found that overall, ECDC activities facilitate informed policy decisions (paragraphs 28 to 30). However a series of joint visits by the Commission and the ECDC to the Member States, which we found to be a useful tool to support their One Health National Action Plans, was progressing slowly due to the lower than anticipated demand from Member States (paragraph 29).

68 The Commission obtains information on AMR through various monitoring activities. However, outcome indicators jointly developed by EU agencies were not consistently used by the Member States we visited, or by the Commission, to monitor progress (paragraphs 31 and 32). EU surveillance data on healthcare associated infections, which are the primary source of infection by resistant bacteria in humans in Europe, is incomplete (paragraphs 33 to 35). Addressing the role of the environment was a specific objective under the Commission's One Health Action Plan. However, at the time of our audit there was insufficient knowledge on the occurrence and spread of AMR in the environment (paragraph 36).

Recommendation 1 – Improving the EU response to AMR through better support to Member State national action plans

The Commission, in consultation with the Member States should:

- (a) promote the results of the JAMRAI and OECD projects, and identify existing funding opportunities to better support the sustained implementation of Member States' AMR One Health policies;
- (b) use outcome indicators to assist Member States to measure their progress in fighting AMR;
- (c) when implementing its new approach to pharmaceuticals in the environment, assess the option of integrating the monitoring of AMR occurrence in the environment into existing environmental monitoring programmes.

Target implementation date: end 2021.

69 The prudent use of veterinary antimicrobials is generally improving and certain Member States have made significant progress in curbing the sales of some antimicrobials for veterinary use. However, there are large differences between the lowest and highest consuming countries, and consumption of some antimicrobials is still too high (paragraphs 38 and 39). The new EU rules for veterinary medicinal products and medicated feed addressed some known weaknesses in the framework

for reducing the consumption of antimicrobials and enhancing surveillance data. However, some challenges remain, including the possible difficulty faced by Member States in collecting data. The future Common Agricultural Policy provides an opportunity to further strengthen the EU framework for dealing with AMR (paragraphs 40 to 43).

70 The monitoring and reporting of the presence of resistant zoonotic and commensal bacteria in certain food of animal origin is the only AMR domain where the Commission has a clear inspection mandate. We found that this monitoring and reporting was generally well implemented, but there are still risk areas which merit consideration for the planned revision of the framework. The Commission inspections led to improvements of Member State systems (paragraphs 44 and 45).

Recommendation 2 – Promoting better monitoring and the prudent use of veterinary antimicrobials

The Commission, in consultation with the Member States should support Member States in developing systems (by defining minimum requirements and considering financial support) that comply with the data collection requirements of the new EU legislation on veterinary medicines.

Target implementation date: end 2022.

71 The Commission, with the EU budget, is one of the world’s largest single investors in AMR research and development. The antimicrobials market lacks commercial incentives to develop new classes of antibiotics. The Commission invested most of this budget in research to find and develop new treatments (via so called “push-mechanisms”) due to the high costs for this type of activity and the reluctance of industry to invest. This research is inherently complex and no breakthrough treatments have yet been brought to the market. We noted that the Commission had not comprehensively evaluated its investments in AMR research (paragraphs 07, 49 and 61).

72 We found delays in certain AMR related projects funded via the public private partnership (i.e. the New Drugs for Bad Bugs programme) which the Commission deployed through JU IMI. There are some interesting products in the research pipeline supported by this programme. Valuable assets have already been created, aiming to speed up the successful development of new antimicrobials, and there are initiatives to sustain them. We consider that the Commission’s One Health Action Plan does not

address some of the specific challenges facing AMR research. For example, it does not cover how to better involve SMEs (which are key in identifying promising new compounds), and how to integrate long term research priorities and sustain activities across funding programming periods (paragraphs 50 to 57).

73 Some antimicrobials that continue to work are withdrawn from the market. The Commission does not have an explicit mandate to propose initiatives to avoid or slow down this process (paragraph 58).

74 Although certain pharmaceutical companies have withdrawn from AMR research, the companies participating under the public private partnership generally maintained their overall commitments (paragraph 60).

75 In order to address the failure of the market to provide new antimicrobials, the Commission has explored economic incentive models (or “pull-mechanisms”) and liaised with stakeholders. By the time of our audit it had not made specific proposals for them (paragraph 61).

Recommendation 3 – Strengthening strategies for boosting AMR research in the EU

The Commission should:

- (a) building on the work already performed, evaluate comprehensively the support it has given to AMR research;
- (b) develop a strategy for its support to AMR research in the context of global and European funding programmes and initiatives, determining how to sustain activities across programming periods and whether new interfaces with SMEs are needed for the discovery of new drugs and clinical development;
- (c) in consultation with the Member States and other stakeholders, further examine how to address market failures affecting the provision of new antimicrobials.

Target implementation date: end 2021 for (a) and end 2022.

This Report was adopted by Chamber I, headed by Mr Nikolaos Milionis, Member of the Court of Auditors, in Luxembourg at its meeting of 9 October 2019.

For the Court of Auditors

Klaus-Heiner Lehne
President

Annexes

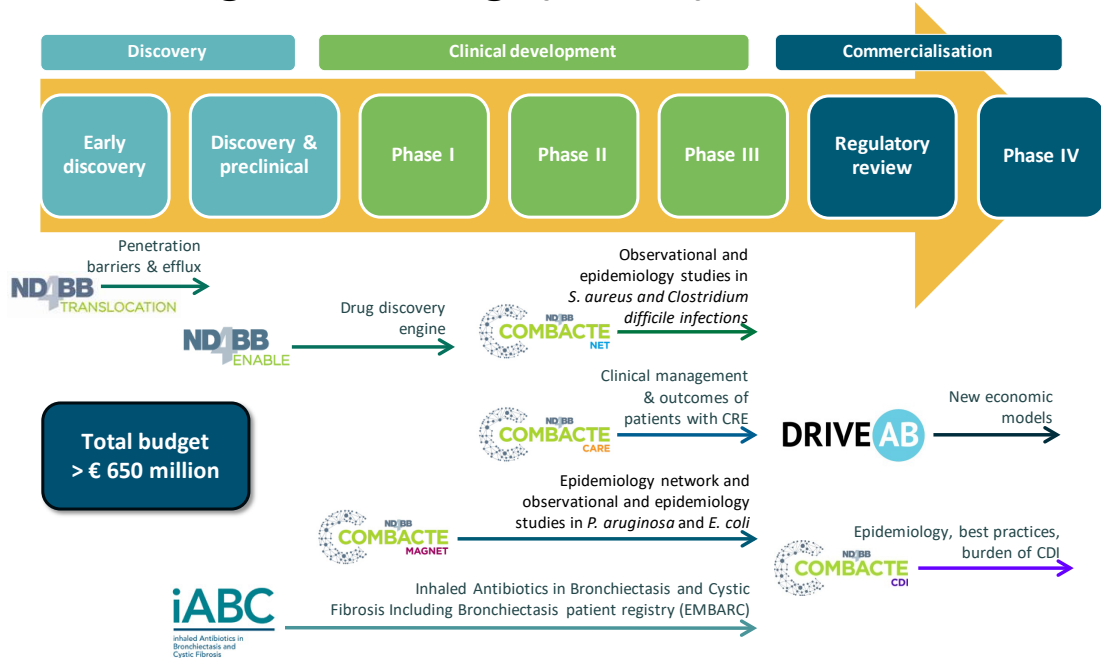
Annex I – Annual sales of veterinary antimicrobial agents for food-producing species, in mg/PCU, for selected European countries, from 2011 to 2016

	2011	2012	2013	2014	2015	2016
Austria	54.5	54.9	57.2	56.3	50.7	46.1
Belgium	175.3	163.1	156.6	158.3	150.1	140.1
Bulgaria	92.6	98.9	116.1	82.9	121.9	155.3
Croatia				113.2	100.0	92.9
Cyprus	407.6	396.5	425.8	391.5	434.2	453.4
Czechia	83.0	79.8	82.2	79.5	68.1	61.2
Denmark	42.6	44.1	44.9	44.2	42.2	40.8
Estonia	70.7	62.9	70.4	77.1	65.2	64.0
Finland	21.9	21.8	22.4	22.3	20.4	18.6
France	116.5	102.7	95.0	107.0	70.2	71.9
Germany	211.5	204.8	179.7	149.3	97.9	89.2
Greece					57.2	63.5
Hungary	192.5	245.8	230.7	193.1	211.4	187.1
Ireland	46.5	55.0	55.9	47.6	51.0	52.1
Italy	371.0	341.0	301.6	332.4	322.0	294.8
Latvia	36.7	41.5	37.7	36.7	37.6	29.9
Lithuania	41.3	39.2	29.1	35.5	35.1	37.7
Luxembourg		43.2	52.1	40.9	34.6	35.5
Netherlands	113.8	74.9	69.9	68.4	64.4	52.7
Poland	127.3	135.2	151.5	140.8	138.9	129.4
Portugal	161.8	156.9	187.2	201.6	170.2	208.0
Romania				109.0	100.5	85.2
Slovakia	43.7	43.3	59.3	65.9	51.0	50.4
Slovenia	46.1	37.0	22.4	33.4	26.4	30.3
Spain	335.8	302.4	317.1	418.8	402.0	362.5
Sweden	13.6	13.5	12.7	11.5	11.8	12.1
United Kingdom	51.1	66.3	62.1	62.1	56.7	45.0

Source: ECA based on European Medicines Agency, 2018, Eighth ESVAC report.

Annex II – ND4BB projects mapped against the drug development process

New Drugs for Bad Bugs (ND4BB)



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Acronyms and abbreviations

AMR: Antimicrobial Resistance

ARHAI: Programme on Antimicrobial Resistance and Healthcare-Associated Infections

CHAFEA: Consumers, Health, Agriculture and Food Executive Agency

DG SANTE: Directorate-General for Health and Food Safety

DG RTD: Directorate-General for Research and Innovation

EARS-Net: European Antimicrobial Resistance Surveillance Network

ECDC: European Centre for Disease Prevention and Control

EFPIA: European Federation of Pharmaceutical Industries and Associations

EFSA: European Food Safety Authority

EMA: European Medicines Agency

EPHA: European Public Health Alliance

ESAC-Net: European Surveillance of Antimicrobial Consumption Network

ESVAC: European Surveillance of Veterinary Antimicrobial Consumption

HAI: Healthcare Associated Infections

HAI-Net: Healthcare-Associated Infections Surveillance Network

JACRA: Joint Interagency Antimicrobial Consumption and Resistance Analysis

JAMRAI: Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections

JPIAMR: Joint Programming Initiative on Antimicrobial Resistance

JU IMI: Joint Undertaking Innovative Medicines Initiative

NAP: National Action Plan

OECD: Organization for Economic Co-operation and Development

SME: Small and medium-sized enterprise

TAFTAR: Transatlantic Taskforce on Antimicrobial Resistance

WHO: World Health Organization

Glossary

Antibiotic: An antimicrobial substance that is active against bacterial infections.

Antibiotic resistance: Occurs when bacteria develops resistance to antibiotics that were designed to kill them.

Antimicrobial: An agent that kills or inhibits the growth of microbial organisms. Examples include antibiotics, antivirals, antimalarials and antifungals.

Antimicrobial resistance: Is the ability of a microorganism (such as bacteria, viruses, some parasites and fungi) to stop an antimicrobial agent from working against it. Microorganisms develop resistance through genetic mutation or acquisition of the genetic information. A natural phenomenon accelerated by the misuse and overuse of antimicrobial medicine.

Broad-spectrum antibiotic: An antibiotic that acts against the two major bacterial groups (gram-positive and gram-negative) or against a wide range of disease-causing bacteria.

European One Health Action Plan against Antimicrobial Resistance: A Commission plan to deliver innovative, effective and sustainable responses to antimicrobial resistance; boost research, promote global action and play a leading role in the fight against AMR.

Gram-negative bacteria: One of the two major bacterial groups. Owing to their impenetrable cell wall and innate ability to mutate and pass on genetic material, these bacteria are increasingly resistant to most of the available antibiotics.

Healthcare associated infections: Infections people get in a medical facility while receiving treatment, which were not present or incubating at the time of their admission.

Health burden: The impact of infections with antibiotic-resistant bacteria measured by longer hospital stays, medical costs, mortality and morbidity.

JAMRAI Work Packages: There are nine work packages: 1. Coordination; 2. Dissemination; 3. Evaluation; 4. Integration in national policies and sustainability; 5. Implementation of one health national strategies and national actions plans for AMR; 6. Prevention of healthcare associated infections; 7. Appropriate use of antimicrobials in humans and animals; 8. Awareness raising and communication; and 9. Prioritizing and implementing research.

Last line antibiotics: The last treatment option for patients infected with bacteria resistant to other available antibiotics.

Metaphylactic use of veterinary antibiotics: This refers to the treatment of a group of animals after the diagnosis of infection in part of the group.

National Action Plan: An action plan developed and adopted by Member State that is aligned with the objectives of the global action plan on antimicrobial resistance.

One Health: A principle, which recognises that the health of human, animal and environment are interconnected.

Serious cross-border health threat: A life- threatening or otherwise serious hazard to health of biological, chemical, environmental or unknown origin which spreads or entails a significant risk of spreading across the national borders of Member States, and which may necessitate coordination at Union level in order to ensure a high level of human health protection.

Superbug: A bacterium that is resistant to the majority of antibiotics commonly used today.

WHO Global Action Plan on Antimicrobial Resistance: The global plan to tackle antimicrobial resistance adopted by the World Health Assembly in 2015 that aims to ensure the ongoing successful treatment and prevention of infectious diseases with effective and safe medicines.

Zoonosis (plural zoonoses): The [infectious diseases](#) caused by bacteria, viruses or parasites that spread from vertebrate animals to humans. Major modern diseases such as [Ebola virus disease](#) and [salmonellosis](#) are zoonoses.

Zoonotic and commensal bacteria: Zoonotic bacteria spread from vertebrate animals to humans; and commensal bacteria live in human hosts typically without causing harm.

REPLIES OF THE COMMISSION TO THE SPECIAL REPORT OF THE EUROPEAN COURT OF AUDITORS

“ADDRESSING ANTIMICROBIAL RESISTANCE: PROGRESS IN THE ANIMAL SECTOR, BUT THIS HEALTH THREAT REMAINS A CHALLENGE FOR THE EU”

EXECUTIVE SUMMARY

III. Member States hold the main responsibility for the organisation and delivery of healthcare.

V The Commission appreciates that the ECA provides ample information about the progress that is being made by the Commission in combatting AMR. This includes the reports from Member States on their evaluation of Commission activities to support their actions on AMR. It is clear from estimates made by ECDC that the health burden of AMR rose between 2007 and 2015.

However, it is too early to tell if this trend has continued. Updated estimates, based on data from 2016-2019 are expected to be available from ECDC in November 2020.

VI The Commission and ECDC provide support to the One Health approach to AMR since mid-2017 as soon as the action plan was adopted.

The Commission and Member States regularly review AMR outcome indicators, published by ECDC, EFSA and EMA. These include levels of resistant infection, AMR mortality and antibiotic consumption, reviewed in the EU Health Security Committee and the AMR One Health Network. In the veterinary sector, sales of veterinary antimicrobial agents are used as an indicator under the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project. The new Regulation (EU) 2019/6 on veterinary medicinal products will strengthen this initiative, by providing for the legal obligation for Member States not only to collect data on sales, but also data on use per species of antimicrobials in animals. This should allow the Member States and the Commission to further target their action against AMR.

The AMR action plan fully recognizes the knowledge gap on the occurrence and spread of AMR in the environment and contains specific actions to close these gaps. Recently, the Commission adopted a communication on the EU strategic approach to pharmaceuticals in the environment which shows the Commission commitment in this area.

VIII With regard to the antimicrobials market, there are many push incentives in place and the existing pharmaceutical legislation provides some pull incentives for innovative medicinal products. The existing landscape has to be taken into account in the discussion about novel incentives or other mechanisms to address market failures with regard to the development and availability of antimicrobials.

The new Regulation (EU) 2019/6 on veterinary medicinal products provides for a simplified assessment procedure and a data protection period, which may be extended up to 18 years under certain conditions. Such provisions intend notably to stimulate the development and enhance the availability of veterinary medicinal products, such as antimicrobial medicinal products.

The Commission has set out its overarching research strategy in its European One Health Action Plan against AMR, and it has funded the JPIAMR Strategic Research and Innovation Agenda.

INTRODUCTION

12 Member States hold the main responsibility for the organisation and delivery of healthcare.

13 Decision (EU) 1082/2013 establishes the Early Warning and Response System (EWRS) and sets out specific criteria for alert notifications of serious cross-border health threats. National competent authorities must notify alerts only when a threat fulfils specific criteria. Thus, not all cases of AMR and healthcare associated infections that fall under epidemiological surveillance would be reported by the EWRS.

Box 1 - The role of EU agencies in AMR

Additionally, EMA supports developers, in particular SMEs and academia and facilitates the development of antibiotics through dedicated schemes for innovative medicines such as the Innovative Task Force activities or the PRIME.¹

OBSERVATIONS

36 The EU one Health action plan against AMR fully recognizes the knowledge gap on the occurrence and spread of AMR in the environment and contains specific actions to close these gaps.

48 With regard to the antimicrobials market, there are many push incentives in place and the existing pharmaceutical legislation provides some pull incentives for innovative medicinal products. The existing landscape has to be taken into account in the discussion about novel incentives or other mechanisms to address market failures with regard to the development and availability of antimicrobials.

49 The Commission has evaluated its financial investment in AMR research and innovation, through the mapping performed by JPIAMR (which was financed via an EU grant). However, the full impact of this investment has not been comprehensively evaluated.

55 The Commission has earmarked funding for the establishment of the new clinical trials network in 2021.

57 The Commission has set out its overarching research strategy in its European One Health Action Plan against AMR, and it has funded the JPIAMR Strategic Research and Innovation Agenda. However, the Commission acknowledges that some of the important challenges facing AMR research are not sufficiently addressed in the strategy.

CONCLUSIONS AND RECOMMENDATIONS

66 The Commission and ECDC provide support to the One Health approach to AMR since mid-2017 when the action plan was adopted. As statistics on outcomes generally take around two years to become available, it is too early to assess impacts or results in terms of reduction in health burden.

68 The Commission and Member States regularly review the AMR outcome indicators which are published by the ECDC, EFSA and EMA. These include levels of resistant infection, AMR mortality and antibiotic consumption which are reviewed in the EU Health Security Committee and in other forums – including the 2019 Romania Presidency Conference on AMR and the AMR One Health Network.

In the veterinary sector, sales of veterinary antimicrobial agents are used as an indicator under the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project. The new Regulation (EU) 2019/6 on veterinary medicinal products will strengthen this initiative, by providing for the legal obligation for Member States not only to collect data on sales, but also data on use per species of antimicrobials in animals. This should allow the Member States and the Commission to further target their action against AMR.

¹ <https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines>
<https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines>

Reporting surveillance data on HAIs to the EU level is an obligation of Member States. ECDC monitors and provides tools for improving such reporting by coordinating point prevalence surveys of HAIs and providing ‘light’ (minimum) surveillance protocols to encourage reporting by all Member States.

The European One Health Action Plan against AMR fully recognizes the knowledge gap on the occurrence and spread of AMR in the environment and contains specific actions to close these gaps. Recently, the Commission adopted a communication on the EU strategic approach to pharmaceuticals in the environment² which shows the Commission commitment in this area.

Recommendation 1 – Improving the EU response to AMR through better support to Member State national action plans

The Commission accepts recommendation 1a

The Commission accepts recommendation 1b.

The Commission accepts recommendation 1c

Recommendation 2 – Promoting better monitoring and the prudent use of veterinary antimicrobials

The Commission accepts recommendation 2.

71 With regard to the antimicrobials market, there are many push incentives in place and the existing pharmaceutical legislation provides some pull incentives for innovative medicinal products. The existing landscape has to be taken into account in the discussion about novel incentives or other mechanisms to address market failures with regard to the development of antimicrobials.

The new Regulation (EU) 2019/6 on veterinary medicinal products provides for a simplified assessment procedure and a data protection period, which may be extended up to 18 years under certain conditions. Such provisions intend notably to stimulate the development and enhance the availability of veterinary medicinal products, such as antimicrobial medicinal products.

72 The Commission has set out its overarching research strategy in its European One Health Action Plan against AMR, and it has funded the JPIAMR Strategic Research and Innovation Agenda. However, the Commission acknowledges that some of the important challenges facing AMR research are not sufficiently addressed in the strategy.

73 Some antibiotics that continue to work are withdrawn from the market. This is a unilateral decision of the pharmaceutical companies where the Commission has limited possibilities to influence them despite efforts to be more proactive.

75 The Commission, is in a process of exploring what kind of initiatives (“pull-mechanisms”) are needed in order to boost development of new antimicrobials. At this stage, the Commission did not put forward any specific proposal, but continues the dialogue with Member States.

Recommendation 3 – Strengthening strategies for boosting AMR research in the EU

The Commission accepts the recommendation.

² COM(2019) 128 of 11/03/2019 http://ec.europa.eu/environment/water/water-dangersub/pdf/strategic_approach_pharmaceuticals_env.PDF

Audit team

The ECA's special reports set out the results of its audits of EU policies and programmes, or of management-related topics from specific budgetary areas. The ECA selects and designs these audit tasks to be of maximum impact by considering the risks to performance or compliance, the level of income or spending involved, forthcoming developments and political and public interest.

This performance audit was carried out by Audit Chamber I Sustainable use of natural resources, headed by ECA Member Nikolaos Milionis. The audit was led by ECA Member Janusz Wojciechowski, then taken over by ECA Member Nikolaos Milionis at the final stage of the report, supported by Kinga Wisniewska-Danek and Kristian Sniter, Heads of Private Office, Katarzyna Radecka-Moroz, Private Office Attaché; Colm Friel, Principal Manager; Stefan Den Engelsen, then Malgorzata Frydel, Head of Task; Anna Zalega, Xavier Demarche and Antonio Caruda Ruiz, Auditors; Frédérique Hussenet, Secretarial Assistant.



From left to right: Anna Zalega, Katarzyna Radecka-Moroz, Nikolaos Milionis, Colm Friel, Malgorzata Frydel, Kristian Sniter, Xavier Demarche.

Timeline

Event	Date
Adoption of Audit Planning Memorandum (APM) / Start of audit	12.12.2018
Official sending of draft report to Commission (or other auditee)	26.7.2019
Adoption of the final report after the adversarial procedure	9.10.2019
Commission's (or other auditee's) official replies received in all languages	EN: 8.11.2019

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Annex II: © UMC Utrecht - COMBACTE project

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Antimicrobial resistance (AMR) is a growing threat to global health. The EU follows a “One Health” approach to the problem, considering veterinary, human health, and environmental issues. We examined how the Commission and relevant EU agencies managed their support to Member States and the EU funded research aimed at fighting antimicrobial resistance. We concluded that the activities of the Commission and agencies led to some progress. However, there is little evidence that the health burden of AMR has reduced. We make recommendations to improve the Commission’s response to AMR through better support to Member State national action plans; promoting better monitoring and the prudent use of antimicrobials; and strengthening strategies for boosting research.

ECA special report pursuant to Article 287(4), second subparagraph, TFEU.



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