



Evaluation of the EC Action Plan against the rising threats from antimicrobial resistance

Final Report

Written by Elta Smith, Catherine A. Lichten, Jirka Taylor, Calum MacLure, Louise Lepetit, Emma Harte, Adam Martin, Ioana Ghiga, Emma Pitchforth, Jon Sussex, Elma Dujso (RAND Europe); Jasper Littmann (Uppsala University)
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Abbreviations and acronyms

AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	antimicrobial resistance
ARHAI	Antimicrobial Resistance and Healthcare-associated Infections (ECDC programme)
ARNA	Antimicrobial resistance and causes of non-prudent use of antibiotics in human medicine (NIVEL programme)
ATC	antibacterial consumption calculator
BEUC	Bureau européen des Unions de Consommateurs (the European consumer organisation)
CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance
CDDEP	Center for Disease Dynamics, Economics & Policy
CHMP	Committee for Medicinal Products for Human Use (part of EMA)
CIA	critically important antimicrobials
COMBACTE	Combatting Bacterial Resistance in Europe
COMBACTE-CARE	COMBACTE — Carbapenem Resistance
COMBACTE-MAGNET	COMBACTE — molecules against Gram negative infections
CVMP	Committee for Medicinal Products for Veterinary Use (part of EMA)
DDD	defined daily doses
DG	Directorate-General
DG DEVCO	Directorate-General for International Cooperation and Development
DG ENV	Directorate-General for Environment
DG RTD	Directorate-General for Research and Innovation
DG SANTE	Directorate-General for Health and Food Safety
Drive AB	Driving reinvestment in research and development and responsible antibiotic use
EAAD	European Antibiotic Awareness Day
EARS-Net	European Antimicrobial Resistance Surveillance Network
EAVI2020	European AIDS Vaccine Initiative 2020
EC	European Commission

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ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EEAS	European External Action Service
EFFORT	Ecology from Farm to Fork Of microbial drug Resistance and Transmission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSA	European Food Safety Authority
EMA	European Medicines Agency (formerly the EMEA)
EMEA	European Medicines Evaluation Agency (now the EMA)
ENABLE	European Gram-negative Antibacterial Engine
EQ	evaluation question
ESAC	European Surveillance of Antimicrobial Consumption (programme)
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption (programme)
EURL-AR	European Reference Laboratory for AMR
FAO	Food and Agriculture Organization of the United Nations
FEFAC	European Feed Manufacturers' Federation
FP7	Seventh Framework Programme for Research and Technological Development
FTE	full-time equivalent
FVE	Federation of Veterinarians of Europe
G7	Group of Seven
GARP	Global Antibiotic Resistance Partnership
GLASS	Global Antimicrobial Resistance Surveillance System
GRACE	Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (programme)
HAI	healthcare-associated infection
HAI-Net	Healthcare-associated Infections Surveillance Network
HALT	Healthcare-associated infections in long-term care facilities (study)
HIV/AIDS	Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome
iABC	Inhaled antibiotics in bronchiectasis and cystic fibrosis

	(programme)
IMI	Innovative Medicines Initiative
INT	interviewee
JPI	Joint Programming Initiative
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LTCV	long-term care facility
MRSA	Meticillin-resistant <i>Staphylococcus aureus</i>
ND4BB	New Drugs for Bad Bugs
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
POST	Parliamentary Office of Science and Technology (UK)
PCU	population correction unit
PPS	point prevalence survey
R&D	research and development
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SME	small and medium-sized enterprise
SSI	surgical-site infection
SWD	Staff working document
TARGET	Treat Antibiotics Responsibly, Guidance, Education, Tools
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
TB	Tuberculosis
TBVAC2020	Tuberculosis Vaccine Initiative 2020
TRANSLOCATION	Molecular basis of the bacterial cell wall permeability (programme)
WHO	World Health Organization
WHO/Europe	World Health Organization Regional Office for Europe

Abstract

The European Commission's 'Action Plan against the Rising Threats from Antimicrobial Resistance' (COM(2011) 748), which covered the period 2011-2016, aimed to address the problem of antimicrobial resistance (AMR) at the European level using a holistic approach. The Directorate-General for Health and Food Safety (DG SANTE) commissioned an evaluation of the 'Action Plan against the Rising Threats from Antimicrobial Resistance' (hereafter, the Action Plan) in 2015 to assess its relevance, effectiveness, efficiency, coherence and added value. The evaluation found that the Action Plan was successful on all of these dimensions and particularly in demonstrating EU political commitment to tackling AMR. EU support made a major contribution to the global AMR research landscape that would likely not have been provided by other sources. The EU should build on progress made and continue to actively address AMR. Recommendations include providing additional coordinated support to Member States, expanding the scope of environmental action and contributing further to international efforts. The EU should sustain support for research and innovation on AMR and should consider the balance of funding among developing new antimicrobials, treatment alternatives and diagnostics. The EU could expand its monitoring and surveillance of AMR and AMR-related activities and better communicate its efforts to stakeholders and the wider public to increase awareness about its work and enable others to learn from the EU example.

Key Messages

This is a summary of findings and recommendations from the evaluation of the European Commission's 'Action Plan against the Rising Threats from Antimicrobial Resistance' (COM(2011) 748). The Action Plan (2011-2016) aimed to address the problem of antimicrobial resistance (AMR) at European level using a holistic approach.

Relevance. The Action Plan fully addressed most needs identified in 2011 and 2015, and it partially addressed needs in three areas: (i) environment, (ii) development of national action plans and (iii) international cooperation. The areas for EU action under the Action Plan were appropriate in view of the distribution of EU and national competences.

Effectiveness. Some progress was observed in national human and animal health policies and performance related to AMR, but implementation varied widely across Member States. The Action Plan enabled new EU policies to help address AMR in animal health, including a new Animal Health Law; the *Guidelines for the Prudent Use of Antimicrobials in Veterinary Medicine*; and proposals on veterinary medicinal products and medicated feed. At present, guidelines on prudent use in human health are being developed. It was too early to link the Action Plan to observed patterns of resistance and antimicrobial usage. The Action Plan helped to strengthen monitoring and surveillance systems, develop and fulfil bilateral and multilateral commitments, and raise public awareness about AMR. Under the Action Plan, EU support for AMR-related R&D increased, and public-private collaboration, open data sharing and coordination of national AMR research efforts were enhanced. Development of antimicrobials was emphasised alongside other research areas. The Action Plan was holistic in its content, but appeared (particularly to external stakeholders) to be more sector-specific in its implementation.

Efficiency. Support for research under the Action Plan was a major contribution to the global AMR research landscape. This support would likely not have been provided by other sources. It was too early to assess the impact and outcomes of ongoing research and innovation activities, because it takes time before R&D efforts deliver results. A lack of available data limited analysis in areas other than research.

Coherence. The Action Plan was coherent with action plans and strategies at national level in the EU and internationally. It was coherent with EU policies in human health, animal health and welfare, food safety, and research. It could have been more coherent with EU environmental policy if it had covered environmental issues more broadly.

Added value. The Action Plan symbolised EU political commitment to AMR, stimulating action in the EU and globally. It helped guide and coordinate national action, especially in research and innovation and in monitoring and surveillance.

Recommendations

In view of the importance of AMR and the EU's role as a leader in addressing this issue, **the EU should build on progress already made and continue to play an active role in this area.**

1. Additional coordinated support should be provided to Member States — to encourage and support Member States in the development and implementation of national action plans and to encourage regional collaboration.

2. The scope of environmental action should be expanded — to better understand the role of the environment in transmission of AMR and to explore what action may be required to reduce associated risks.

3. The EU should contribute further to international efforts — continuing international cooperation, in particular with the WHO, to determine the potential for supporting a global approach and to improve monitoring and surveillance across the European region.

4. The EU should sustain its support for AMR research and innovation activities — and consider, in collaboration with the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), the focus of the AMR research portfolio.

5. The EU could expand its monitoring of AMR and of AMR-related activities — taking a more holistic, data-driven approach, linking data on resistance to and usage of antimicrobials to prescribing trends and other factors; better tracking AMR-related costs and benefits; considering the use of targets and related indicators, including, as appropriate, country-specific targets and indicators; and continuing to monitor public awareness.

6. The EU institutions and agencies could better communicate their efforts to stakeholders and the wider public — to increase awareness about their cross-sectoral work and other activities and to enable other countries and organisations to learn from the EU's example.

EXECUTIVE SUMMARY

Introduction

This is the final report for the evaluation of the European Commission's 'Communication to the European Parliament and the Council on the Action Plan against the Rising Threats from Antimicrobial Resistance' (COM(2011) 748) (hereafter, the Action Plan). It presents the analysis of and conclusions to 10 evaluation questions set out in the project terms of reference.

Context to the evaluation

Antimicrobials are drugs that treat infections caused by bacteria, viruses, fungi and parasites. They treat common infections and minor injuries that in the past were life-threatening. They have reduced the incidence of tuberculosis dramatically, enabled epidemic and pandemic treatment of influenza, supported Human Immunodeficiency Virus (HIV) treatment and reduced the health burden caused by malaria. Antimicrobials are also crucial for controlling infection in healthcare settings and enable the successful delivery of many health interventions, including routine operations. These achievements are being threatened by increasing resistance to antimicrobials, where once-effective treatments either no longer work or do not work as well as they originally did.

Antimicrobial resistance (AMR) is a naturally occurring phenomenon, but the use of antimicrobials has also led to resistance, where micro-organisms evolve abilities to survive drugs intended to kill them or stop their growth. AMR has been an issue since antibiotics were introduced, but the challenges it brings are now compounded by an increase in resistance and a lack of new antimicrobial agents being developed.

AMR can pass between animal and human populations, and it can spread in the environment. As a result, tackling AMR requires a broad approach that addresses the use of antimicrobials in veterinary medicine (both in livestock and pets); in human medicine; and in environments where resistant bacteria can accumulate, such as wastewater systems. This has led to adoption of the 'one health' approach, which brings together animal health, human health and the environment as interconnected areas that are important for addressing AMR. Addressing these areas together requires collaboration by multiple actors: veterinarians, clinicians and others. The 'one health' approach has been promoted by the European Union (EU) since 2008.

The EU AMR Action Plan

While efforts to tackle AMR at the EU level predate the Action Plan, the Action Plan brought together interested parties from across Europe to identify objectives and related measures to be implemented by 2016 to address AMR issues. The Action Plan was developed on the basis of scientific opinions on AMR from EU risk assessment bodies, including the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), the European Medicines Agency (EMA) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).

The Action Plan addressed the problem of AMR at European level across the following areas: monitoring and surveillance; appropriate use of antimicrobials; infection prevention; development of new antimicrobials, alternative treatments and diagnostic tools; improving understanding of AMR; and reinforcement and coordination of research efforts. The objectives also covered international cooperation and awareness, education and training. The plan was designed to take a holistic approach across multiple sectors, covering human and veterinary aspects to protect both human and animal health. The EC Action Plan on AMR was published in 2011 and covered a five-year period, through to 2016.

The Action Plan evaluation

The evaluation objectives were to analyse whether the actions set out in the Action Plan were the most appropriate actions to be taken to combat AMR, and which elements worked well or not (and why). The objectives also included assessing whether the objectives were still relevant to the needs in tackling AMR and whether the approach was appropriately holistic.

The scope of the evaluation included the 12 strategic actions and 7 core objectives set out in the Action Plan. It covered the period 2011-2015 in all 28 EU Member States and included an assessment of activities undertaken in relation to the Action Plan for all stakeholder groups involved in its implementation. In addition to assessing the impact of the Action Plan, the evaluation identified areas where actions could be improved in the future.

This evaluation, commissioned by the Directorate-General for Health and Food Safety (DG SANTE) in September 2015, was delivered by RAND Europe, working with a team of five experts covering the human health, animal health, and research and innovation aspects of AMR.

Evaluation methods

The evaluation involved a mixed-methods approach:

- Two **online surveys**, targeting (i) EU-28 Member State representatives responsible for areas related to AMR and (ii) individual stakeholders and stakeholder organisations in areas related to AMR, including animal and human health, food safety, agriculture, public awareness, and research and innovation. Both surveys targeted respondents with expertise in animal and/or human health.
- An online **public consultation** run on the Commission's 'Your Voice in Europe' website in accordance with EU guidelines.
- In-depth **interviews** with representatives of the European Commission, European agencies, international organisations, EU-level interest groups and researchers.
- Two day-long **workshops** to inform stakeholders about the evaluation and emerging findings and to obtain evidence about AMR-related changes and the Action Plan's impact.
- **Desk research** to collect information from sources including legislative documents, scientific guidelines, surveillance data, public surveys, stakeholder reports and academic literature.
- Eight **case studies** that explored specific AMR issues, informed by desk research and interviews.

Conclusions

Overall, the EC Action Plan helped bring about improvements in the situation on AMR in the EU that would not have happened otherwise. Furthermore, the EC Action Plan identified actions best dealt with at EU level. The Action Plan delivered added value in two important ways:

- The Action Plan acted as a symbol of EU political commitment and stimulated actions at the EU and global levels.
- The Action Plan provided a framework to guide and coordinate national activities on AMR, enabling those activities to be more effective than they would have been otherwise. Areas that clearly benefitted from improved international coordination were (i) research and innovation, particularly through the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)

and (ii) monitoring and surveillance (for example, through joint analysis of animal and human consumption and resistance data and through full harmonisation in the veterinary field).

The Action Plan captured a 'one health' approach, bringing together actions to address human and animal health and, to a lesser extent, the environment, thus addressing the problems identified in 2011.

It was too early to identify impacts of the Action Plan on antimicrobial consumption or resistance in humans and animals. During the period of the Action Plan, however, policies for prudent use and to strengthen infection prevention in both humans and animals were developed, implemented and evaluated. For the example, an evaluation was conducted on implementation of the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections (2009/C 151/01) (Council of the EU 2009) and of the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC) (Council of the EU 2002). A new EU Animal Health Law was adopted, and the Commission issued legislative proposals on veterinary medicines and medicated feed and published its *Guidelines for the Prudent Use of Antimicrobials in Veterinary Medicine* (2015/C 299/04) (EC 2015b).

Variability was observed across Member States in terms of patterns of drug usage, occurrence of resistance, and the extent to which policies had been introduced and implemented to tackle AMR. This issue was a particular challenge in the areas related to human health, where Member States are responsible for action and EU competence is limited.

Major developments in mechanisms to support and coordinate research and innovation were attributable to the Action Plan (such as the JPIAMR). Although it was too early to assess longer-term outcomes for addressing AMR, the EU increased its funding for AMR-related research, for instance, through the New Drugs for bad Bugs (ND4BB) programme to incentivise development of new treatments, and that AMR became a priority under the Innovative Medicines Initiative (IMI).

Relevance

To what extent do the objectives of the Action Plan address the problems identified in 2011? How well do these objectives still correspond to the current needs of tackling AMR in the EU?

- In total, 78 % of survey respondents agreed or strongly agreed that the EC Action Plan helped bring about improvements in the situation on AMR in the EU that would not have happened otherwise.
- The Action Plan's objectives addressed the problems identified in 2011 to a large extent and were relevant to the needs identified in 2011 according to more than 80 % of survey respondents across most Action Plan objectives.
- The objectives set in 2011 correspond to current needs and are considered to be even more relevant due to wider recognition that AMR is a serious global health threat.

Survey respondents and workshop participants highlighted the following particular issues:

- International cooperation. Although EU-supported AMR programmes and activities contributed to international initiatives, it was stressed that the international dimension of AMR is growing in importance. Therefore, there is a need to strengthen existing international initiatives, such as monitoring AMR and antimicrobial usage and the availability and quality of antimicrobials.

- AMR-related research. The Action Plan addressed the need to support AMR-related research, including vaccines, diagnostics and other treatments. However, survey respondents emphasized that more financial assistance is needed in the areas of vaccines, diagnostics and other treatments.
- AMR in the environment. Although the EC Action Plan addressed environmental pollution from antimicrobial manufacturing (under action 8), it did not cover the need to improve understanding of how AMR could emerge and spread from animal waste and human sewage in water and soil. Therefore, the role of the environment in the spread of AMR needs to be further explored.
- Development of national action plans:
 - 18 EU Member States have a national AMR strategy, 17 of which have a formal Action Plan to tackle AMR.
 - There was no specific action or support mechanism related to this in the Action Plan. However, the EU's *Guidelines for the Prudent Use of Antimicrobials in Veterinary Medicine*, published in 2015, call for holistic strategies and/or action plans to be put in place.

Are the areas for EU action appropriate in view of the distribution of EU and national competences?

In total, 84 % of Member State and stakeholder survey respondents agreed or strongly agreed that the EC Action Plan identified actions best dealt with at EU level. The EU has greater policy competence with respect to animal health policies than it does with respect to human health policies. Responsibility for research and innovation is shared by the EU and Member States; research and innovation actions have centred on EU action to support research and assist Member States and other countries with coordinating their AMR research programmes.

Effectiveness

To what extent have the actions been effective at improving treatment of infections in humans and animals?

Antimicrobial consumption in humans and animals

The Action Plan played a role in helping to contain the consumption of antimicrobials through the achievement of policy objectives for human and animal health. Changes in the consumption of antimicrobials for use in humans or animals could not be linked to the Action Plan, however, for two reasons. First, at the time of this evaluation, it was too early for changes attributable to the Action Plan to be observed and reported. Second, the effects of the Action Plan could not be disentangled from the effects of other AMR policy initiatives that were taking place prior to and in parallel with the Action Plan. Variability was observed across Member States in terms of patterns of drug usage in human and animals.

During the period of the Action Plan, the following policies for the treatment of infection in both humans and animals were developed, implemented and/or evaluated:

- The Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine and the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections were evaluated. The evaluations showed that there have been improvements related to the implementation of prescription-only requirements for antimicrobials; education and training for healthcare workers on AMR; and, to a lesser extent, antimicrobial stewardship and the implementation of control measures against AMR in nursing homes and long-term care facilities (LTCFs). Guidelines on prudent use in human health were being developed at the time of the evaluation.

- The Commission introduced guidelines in 2015 on the prudent use of antimicrobials in veterinary medicine. The Commission also adopted proposals on veterinary medicinal products and medicated feed in 2014 (undergoing the ordinary legislative procedure at the time of the evaluation). The guidelines and legislative proposals were widely expected to promote appropriate use of veterinary antimicrobials.
- EU monitoring and surveillance systems regarding the consumption of antimicrobials were strengthened. The coverage and scope of data collected improved, both for the European Surveillance of Antimicrobial Consumption (ESAC) network of national surveillance systems on antimicrobial consumption in humans and for the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, which gathers sales data on antimicrobials intended for veterinary use.

Research and development

Research and development was a major focus of the Action Plan, and progress was made in this area at policy level, although it was too early to assess the impact and outcomes:

- Further support for AMR research was achieved through the Seventh Framework Programme for Research and Technological Development (FP7) and the Horizon 2020 framework programme.
- AMR became one of the 12 priorities of the public-private IMI.
- The ND4BB programme was launched to spur the development of new antibiotics along the value chain, from basic science to new business models, and created conditions for open data sharing.
- Improvements in coordination were achieved across countries through the JPIAMR.

To what extent have the actions aimed at containing the risks of spreading AMR been effective?

The Action Plan played a role in helping to contain the risks of spreading AMR, and it did so through policy achievements, including new legislation. However, changes in the occurrence of AMR in humans or animals could not be linked to the Action Plan, for two reasons: (i) at the time of this evaluation, it was too early for changes attributable to the Action Plan to be observed and reported and (ii) the effects of the Action Plan could not be disentangled from the effects of other AMR policy initiatives that were taking place prior to and in parallel with the Action Plan. Variability was observed across Member States in terms of patterns of resistance in human and animals.

During the period of the Action Plan, the following main policies regarding the risk of spreading AMR were developed, implemented and/or evaluated:

- The Animal Health Law was adopted by the European Parliament and Council in March 2016. The law introduces the legal basis for the monitoring of antimicrobial resistance in animal pathogens and is viewed as an important step towards better infection prevention.
- EU monitoring and surveillance systems were strengthened. The coverage and scope of data collected by the European Antimicrobial Resistance Surveillance Network (EARS-Net) improved. Furthermore, Decision 2013/652/EC on monitoring and reporting of AMR extended the coverage and scope of data collected on zoonotic and commensal bacteria in food-producing animals and in certain foods.
- International cooperation was strengthened through EU-supported AMR initiatives, such as the JPIAMR and the European Reference Laboratory for AMR (EURL-AR). The EU contributed to the development of the WHO global Action

Plan; the Global Foodborne Infections Network; World Organisation for Animal Health (OIE) standards; the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR); the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (part of the Codex Alimentarius); and work with the Organisation for Economic Co-operation and Development (OECD), China and the Russian Federation.

- Communication was strengthened through European Antibiotic Awareness Day (EAAD), which supported and fostered the development of national AMR awareness campaigns, and it may have also helped raise awareness among policymakers and public health professionals. Nevertheless, limited improvement was observed in public awareness about AMR across the EU, as measured by the Eurobarometer survey.

To what extent has the coverage of actions across different services (that is, Directorate-Generals) within the European Commission been effective in capturing the holistic approach and in delivering results?

In total, 98 % of the survey respondents agreed with the need to take a holistic approach to addressing AMR. Furthermore, 63 % of Member State and stakeholder survey respondents agreed that the EC Action Plan captured this holistic approach. Overall:

- The Action Plan was viewed as being holistic in its content, but more sector-specific in its implementation.
- The role of the environment on AMR should be further explored.
- Implementation of the Action Plan involved collaboration across Directorate-Generals (DGs) and agencies, but that collaboration was less visible to external stakeholders.

Efficiency

Has the EU budget been efficiently used to address the objectives of the Action Plan?

Limited data were available on EU expenditure for activities other than research, which severely limited the potential to assess efficiency. Expenditure specifically on research was in line with the objectives of the Action Plan, and EU support constituted a valuable contribution to the AMR research funding landscape that would likely not have been provided by other sources. It was not possible to assess the impact and outcomes of ongoing research and innovation activities, because it takes time before research and development (R&D) efforts deliver results.

Coherence

To what extent is the Action Plan coherent with Member States' relevant national (or regional) strategies and action plans and with similar initiatives at the international level?

The Action Plan is to a large extent coherent with Member States' relevant national or regional strategies and action plans. It helped galvanise Member State action on AMR and influenced some national-level action plans according to 56 % of Member State representatives who responded to the survey. Furthermore, 61 % indicated that their national plan and the EC Action Plan have a similar scope, 26 % replied that the EC Action Plan has a broader scope, and 8 % replied that the national policy has a broader scope, mainly regarding environmental issues.

EU collaboration with non-EU partners, including the United States of America, Canada and Norway, was aligned with the EC Action Plan through TATFAR. Furthermore, the EC Action Plan was broadly coherent with the WHO global Action Plan and with the WHO Regional office for Europe (WHO/Europe) Action Plan.

To what extent are the actions contained in the Action Plan coherent with other EU policies on the environment, human health, animal health and welfare, food safety, agriculture, research, competitiveness and SMEs [small and medium-sized enterprises]?

According to Member State and stakeholder survey respondents, EU AMR policies complemented or reinforced existing EU policies in the following areas: human health (78 %), animal health and welfare (80 %), food safety (75 %) and research (77 %).

Regarding the environment, only 56 % of survey respondents agreed or strongly agreed that EU AMR policy complemented or reinforced EU policy on the environment. While the Action Plan was not inconsistent with EU policy on the environment, it could have been more coherent if the breadth of its coverage of environmental issues had encompassed a wider range of issues, including the impacts of agricultural and human waste on AMR transmission.

Added value

What is the added value resulting from the EC Action Plan compared with what could be achieved by Member States at national and/or regional levels? Did the EC Action Plan identify the actions which should be best dealt with at EU level?

Overall, 84 % of Member State and stakeholder survey respondents agreed or strongly agreed that the Action Plan identified actions best dealt with at EU level. The Action Plan delivered added value to tackle AMR in two important ways:

- The Action Plan acted as a symbol of EU political commitment and stimulated action at the EU and global levels.
- The Action Plan provided a framework to guide and coordinate national activities on AMR, enabling those activities to be more effective than they would have been otherwise. Areas that clearly benefitted from improved international coordination were (i) research and innovation and (ii) monitoring and surveillance.

To what extent can improvements in the situation on AMR (outcomes and other changes identified in previous evaluation questions) be associated with the development and implementation of the EC Action Plan?

Member State and stakeholder survey respondents agreed or strongly agreed (78 %) that the EC Action Plan helped bring about improvement in AMR that would not have happened otherwise. Progress included:

- The development of new EU policies and guidance, including the new Animal Health Law; the *Guidelines for the Prudent Use of Antimicrobials in Veterinary Medicine*; proposals for veterinary medicinal products and medicated feed; and the development of guidelines for prudent use in human health;
- An increase in global awareness about AMR and contribution to international coordination efforts regarding R&D and monitoring and surveillance;
- Harmonisation, integration, improved quality and improved coverage of monitoring and surveillance data on antimicrobial consumption and resistance across the EU;
- The organisation of national awareness campaigns in some Member States, stimulated by the EU's EAAD — an initiative which predated and continued under the Action Plan; and
- EU funding for AMR-related R&D, which increased under the Action Plan; in terms of worldwide expenditure on AMR-related R&D, EU funds represented a significant source of public funding.

Recommendations

AMR remains a pressing problem in the EU and internationally. The Action Plan played an important role in symbolising and galvanising action on AMR issues within the EU and encouraged engagement with third countries and the international community to tackle AMR. The EU should build on progress already made and continue to play an active role in this area, in line with the following recommendations:

1. Additional, coordinated support should be provided to Member States.

Consumption of antimicrobials and levels of resistance were highly variable across Member States. Therefore, a one-size-fits-all approach to addressing this issue is insufficient. Both funding and technical support are likely to be required, particularly for those countries lagging behind. Future EU action could include a mechanism to encourage and support Member States in the development and implementation of national action plans.

2. The scope of environmental action should be expanded.

There is a need to improve understanding of the role of the environment in the emergence and transmission of resistance through animal, human and manufacturing waste in water and soil and to explore what action may be required to reduce associated risks. The Directorate-General for Environment (DG ENV) should play a role in the design and implementation of future action in this area.

3. The EU should contribute further to international efforts.

Given that the international dimension of AMR is growing in importance, the EU should strengthen existing international cooperation activities related to developing systems for global surveillance. This would help to address the challenges associated with increased migration, tourism and trade, which carry with them the potential to further spread AMR in the EU and beyond. The EU should continue international cooperation, in particular with the WHO, in the area of monitoring and surveillance.

4. The EU should sustain support for research and innovation activities.

Research and innovation activities related to AMR are an area where the EU has played an important role globally. Critical funding extended to research activities was catalysed by the Action Plan. The EU should sustain support for the projects and programmes that have been introduced.

In collaboration with the JPIAMR, the Commission should also consider which topics should be covered by EU funding, in particular on research related to diagnostics, vaccines, alternatives to antimicrobials for treating infection, social and behavioural factors that drive antimicrobial usage and the interplay between the environment and AMR.

5. The EU could expand its monitoring of AMR and of AMR-related activities.

Improvements in the monitoring and surveillance of AMR and antimicrobial usage were a major success of the Action Plan. The Eurobarometer survey also provided an important source of data on public awareness of AMR in the EU. Limited availability of data on AMR-related expenditures impaired transparency about the costs associated with addressing AMR within the EU. There are steps that can be taken in each of these areas:

- The EU should continue to support a more holistic system for monitoring AMR issues, linking data on resistance, consumption and sales of antimicrobials to prescribing trends and other factors in human and animal health — and

potentially extending to the environment. Such a system would provide a more complete picture of the AMR situation and help to pinpoint problem areas.

- Targets and related indicators could be introduced, including, as appropriate, country-specific targets and indicators to ensure that information is being collected about progress on AMR issues related to shorter-term activities, outputs and outcomes in order to assist in assessing progress and linking it to longer-term outcomes and impacts. Targets related to longer-term indicators, such as usage of antimicrobials or occurrence of resistance, could also be considered.
 - Monitoring cost-effectiveness to ensure adequate financial investments are made in measures to address AMR globally.
 - Monitoring of public awareness should continue; the EU should continue to support awareness-raising activities through European Antibiotic Awareness Day.
6. The EU institutions and agencies could better communicate their efforts to stakeholders and the wider public.

The Action Plan successfully brought together in one policy instrument actions related to animal health and welfare, food safety and human health, in line with the 'one health' approach. The Commission and its agencies collaborated across DGs and agencies to implement the Action Plan. While some collaborative activities were highly visible, such as interagency reporting, external stakeholders were less aware of the collaboration taking place within the Commission. Accordingly:

- The Commission could better communicate to increase awareness about its cross-sectorial work and other activities and its relationship to the Action Plan. Such communication would enable other countries and organisations to learn from the approach being taken by the EU.
- This collaborative approach could also extend to encouraging interaction among stakeholders representing different sectors that are involved in addressing AMR but that historically have not interacted.

RÉSUMÉ EXÉCUTIF

Introduction

Ceci est le rapport final de l'évaluation de la Communication de la Commission Européenne au Parlement Européen et au Conseil sur le Plan d'action pour combattre les menaces croissantes de la résistance aux antimicrobiens (ci-après dénommé plan d'action). Il présente l'analyse et les conclusions des dix questions d'évaluation décrites dans les termes de référence du projet.

Contexte de l'évaluation

Les antimicrobiens sont des médicaments traitant les infections causées par des bactéries, virus, champignons et parasites. Ils traitent les infections communes et blessures mineures qui auparavant menaçaient des vies. Ils ont radicalement réduit le nombre de cas de tuberculose, ont permis le traitement épidémique et pandémique de la grippe, ont encouragé le traitement contre le sida et réduit le fardeau causé par le paludisme. Les antimicrobiens sont également cruciaux pour le contrôle des infections dans les établissements de santé et pour permettre le succès des interventions médicales, notamment les opérations de routine. Ces réussites sont menacées par l'accroissement de la résistance aux antimicrobiens, là où des traitements auparavant efficaces ne fonctionnent plus ou ne fonctionnent plus aussi bien qu'initialement.

La résistance aux antimicrobiens est un phénomène se produisant naturellement, mais l'utilisation d'antimicrobiens a aussi accru la résistance, là où des micro-organismes ont évolué et développé des capacités à survivre aux médicaments devant les tuer ou arrêter leur croissance. La résistance aux antimicrobiens est un problème depuis l'introduction des antibiotiques, mais les défis qu'elle amène sont à présent amplifiés par l'accroissement de la résistance et le manque d'agents antimicrobiens étant développés.

La résistance aux antimicrobiens peut se transmettre de la population animale à la population humaine et se propager dans l'environnement. Par conséquent, s'attaquer à la résistance aux antimicrobiens requiert une approche générale s'intéressant à l'utilisation des antimicrobiens en médecine vétérinaire, à la fois pour le bétail et pour les animaux domestiques, en médecine humaine, ainsi qu'aux environnements dans lesquels les bactéries résistantes peuvent s'accumuler, tels que les systèmes d'évacuation des eaux usées. Ceci a conduit à l'adoption de l'approche 'One Health' qui rassemble les domaines de la santé animale, la santé humaine et l'environnement dont l'interconnexion est importante pour pallier la résistance aux antimicrobiens. Le terme implique également la collaboration de multiples acteurs (vétérinaires, cliniciens et autres) afin de s'occuper de ces domaines simultanément. L'approche 'One Health' est soutenue par l'Union Européenne (UE) depuis 2008.

Le plan d'action européen pour combattre les menaces croissantes de la résistance aux antimicrobiens

Tandis que les efforts pour lutter contre la résistance aux antimicrobiens au niveau européen sont antérieurs au plan d'action, ce dernier rassemble les parties intéressées de toute l'Europe afin d'identifier les objectifs et les mesures associées devant être mises en place d'ici à 2016 et permettant de résoudre les défis liés à la résistance aux antimicrobiens. Le plan d'action a été développé sur la base d'opinions scientifiques sur la résistance aux antimicrobiens provenant des organes européens d'évaluation des risques, y compris le Centre Européen pour la Prévention et le Contrôle des Maladies (CEPCM), l'Autorité Européenne de Sécurité des Aliments (AESAs), l'Agence Européenne des Médicaments et le Comité Scientifique des Risques Sanitaires Emergents et Nouveaux (CSRSEN).

Le plan d'action répond au problème de la résistance aux antimicrobiens au niveau européen dans les domaines suivants: suivi et surveillance, utilisation appropriée des

antimicrobiens, prévention des infections, développement de nouveaux antimicrobiens et de traitements alternatifs et développement d'outils de diagnostic, amélioration la compréhension de la résistance aux antimicrobiens et renforcement et coordination des efforts de recherche. Les objectifs couvrent également la coopération internationale et la sensibilisation, l'éducation et la formation. Le plan d'action a été conçu pour adopter une approche holistique au travers de multiples secteurs, recouvrant les aspects humains et vétérinaires afin de protéger à la fois la santé humaine et animale. Le plan d'action européen pour combattre les menaces croissantes de la résistance aux antimicrobiens fut publié en 2011 et a couvert une période de cinq ans jusqu'en 2016.

L'évaluation du plan d'action

Les objectifs de l'évaluation étaient d'analyser si les actions décrites dans le plan d'action étaient les actions les plus appropriées à prendre pour combattre la résistance aux antimicrobiens, et quels éléments ont bien fonctionné ou non (et pourquoi). Les objectifs de l'évaluation incluaient également une évaluation de la pertinence des objectifs du plan d'action pour les besoins associés à la lutte contre la résistance aux antimicrobiens, et si l'approche holistique était suffisamment pertinente.

Le cadre de l'évaluation incluait les 12 actions stratégiques et sept objectifs principaux décrits dans le plan d'action. Elle a couvert la période 2011-2015 sur l'ensemble des 28 Etats Membres de l'UE, and a inclus une évaluation des activités entreprises en relation avec le plan d'action et pour tous les groupes de parties intéressées impliqués dans sa mise en œuvre. En plus d'évaluer l'impact du plan d'action, l'évaluation a identifié les domaines dans lesquels les actions pourraient être améliorées dans le futur.

Cette évaluation, commandée par la Direction Générale Santé et Sécurité Alimentaire (DG SANTE) en Septembre 2015, a été réalisée par la RAND Europe travaillant avec une équipe de cinq experts couvrant les aspects de la résistance aux antimicrobiens liés à la santé humaine, la santé animale et la recherche et l'innovation.

Méthodes d'évaluation

Cette évaluation a impliqué une approche méthodologique mixte :

- Deux **enquêtes en ligne** ciblant i) des représentants des 28 Etats Membres de l'UE responsables de domaines liés à la résistance aux antimicrobiens et ii) des acteurs individuels et des organisations de parties prenantes dans les domaines liés à la résistance aux antimicrobiens, y compris la santé animale et humaine, la sécurité alimentaire, l'agriculture, la sensibilisation du public et la recherche et l'innovation. Les deux enquêtes ont ciblé des personnes ayant une expertise en santé animale et/ou humaine.
- Une **consultation publique** a été lancée sur le site internet 'Your Voice in Europe' de la Commission conformément avec les lignes directrices de l'UE.
- Des **entretiens** approfondis avec des représentants de la Commission Européenne, des agences européennes, des organisations internationales, des groupes d'intérêt opérant au niveau de l'UE et des chercheurs.
- Deux **ateliers de travail** d'une journée afin d'informer les parties intéressées sur l'évaluation et les premières conclusions, et obtenir des indications sur les changements liés à la résistance aux antimicrobiens et sur l'impact du plan d'action.
- Des **recherches documentaires** pour récolter des informations de sources différentes, notamment des documents législatifs, des lignes directrices

scientifiques, des données de surveillance, des enquêtes publiques, des rapports de parties intéressées et de la littérature universitaire.

- Huit **études de cas** analysant des problèmes spécifiques de la résistance aux antimicrobiens, renseignés par des recherches documentaires et des entretiens.

Conclusions

Dans l'ensemble le plan d'action de la Commission Européenne a apporté des améliorations à la situation de la résistance aux antimicrobiens dans l'UE qui n'auraient pas pu se produire autrement. De plus, le plan d'action de la Commission Européenne a identifié les actions les mieux prises en charge au niveau européen. Le plan d'action a apporté une valeur ajoutée de deux manières importantes :

- Le plan d'action a agi comme un symbole de l'engagement politique de l'UE et a stimulé des actions au niveau européen et mondial.
- Le plan d'action a fourni un cadre pour guider et coordonner les activités nationales de lutte contre la résistance aux antimicrobiens, permettant à ces activités d'être plus efficaces qu'elles ne l'auraient été autrement. Les domaines ayant clairement bénéficié d'une amélioration de la coordination internationale ont été ceux de la recherche et de l'innovation, particulièrement au travers de l'Initiative de Programmation Conjointe sur la résistance aux antimicrobiens (JPIAMR) ainsi que les domaines du suivi et de la surveillance (par exemple au travers de l'analyse jointe de la consommation d'antimicrobiens et des données de surveillance pour les animaux et les humains et au travers de l'harmonisation complète du domaine vétérinaire).

Le plan d'action a emprunté une approche 'One Health', rassemblant des actions s'intéressant à la santé humaine et animale et, dans une moindre mesure, à l'environnement, répondant aux problèmes identifiés en 2011.

Il était trop tôt pour identifier les impacts du plan d'action sur la consommation d'antimicrobiens ou la résistance chez les humains et les animaux. Au cours de la période de mise en œuvre du plan d'action, des politiques pour l'usage prudent et raisonné et pour renforcer la prévention des infections à la fois chez les humains et les animaux ont cependant été développées, mises en place et évaluées. A titre d'exemple, une évaluation a été conduite sur la mise en œuvre de la recommandation du Conseil relative à la sécurité des patients et de la recommandation du Conseil relative à l'utilisation prudente des agents antimicrobiens en médecine humaine. Une nouvelle législation de l'UE sur la santé animale a été adoptée et la Commission a présenté des propositions législatives sur les médecines vétérinaires et aliments médicamenteux, et a publié des lignes directrices pour une utilisation prudente des antimicrobiens en médecine vétérinaire.

Une certaine variabilité a été observée entre les Etats Membres en termes d'utilisation des médicaments, la présence de résistance et le degré d'introduction et de mise en œuvre de politiques visant à combattre la résistance aux antimicrobiens. Cet aspect a représenté un défi particulièrement dans les domaines liés à la santé humaine, où les Etats Membres sont responsables de mettre en place des actions et la compétence de l'UE est limitée.

Des développements majeurs dans les mécanismes de soutien et de coordination de la recherche et de l'innovation ont été attribués au plan d'action (tel que la JPIAMR). Bien qu'il soit prématuré d'évaluer les résultats de long-terme sur la résistance aux antimicrobiens, l'UE a augmenté ses financements pour la recherche liée à la résistance aux antimicrobiens, par exemple au travers du programme « New Drugs for bad Bugs » (ND4BB), afin d'encourager le développement de nouveaux traitements.

La résistance aux antimicrobiens est également devenue une priorité sous l'initiative en matière de médicaments innovants (IMI).

Pertinence

Dans quelle mesure les objectifs du plan d'action répondent-ils aux problèmes identifiés en 2011? De quelle manière ces objectifs correspondent-ils toujours aux problèmes actuels de la lutte contre la résistance aux antimicrobiens dans l'UE ?

- Au total, 78 pour cent des personnes interrogées lors des enquêtes étaient d'accord ou tout-à-fait d'accord que le plan d'action de la Commission Européenne a apporté des améliorations à la situation de la résistance aux antimicrobiens dans l'UE qui n'auraient pas pu se produire autrement ;
- Les objectifs du plan d'action répondent, dans une large mesure, aux problèmes identifiés en 2011, pour la plupart des objectifs du plan d'action selon plus de 80 pour cent des personnes interrogées ; et
- Les objectifs fixés en 2011 correspondent aux besoins actuels et sont même considérés comme d'autant plus pertinents dû à la reconnaissance plus large de la menace mondiale représentée par la résistance aux antimicrobiens.

Les personnes interrogées dans les enquêtes et les participants aux ateliers de travail ont en particulier souligné les aspects suivants :

- La coopération internationale : Bien que les programmes et activités soutenus par l'UE et liés à la résistance aux antimicrobiens ont contribué aux initiatives internationales, il a été souligné que la dimension internationale de la résistance aux antimicrobiens croît en importance. Par conséquent, il est nécessaire de renforcer les initiatives internationales existantes, telles que le suivi de la résistance aux antimicrobiens et de la consommation d'antimicrobiens ainsi que de la disponibilité et de la qualité des antimicrobiens.
- La recherche liée à la résistance aux antimicrobiens : Le plan d'action répond au besoin de soutenir la recherche liée à la résistance aux antimicrobiens, notamment sur les vaccins, diagnostiques et autres traitements. Cependant les personnes interrogées ont souligné que davantage d'assistance financière est nécessaire concernant le développement de vaccins, diagnostiques et autres traitements.
- La résistance aux antimicrobiens dans l'environnement : Bien que le plan d'action de la Commission Européenne s'intéresse à la pollution environnementale provenant de la fabrication d'antimicrobiens, il ne concerne pas les aspects liés à l'amélioration de la compréhension de la manière dont la résistance antimicrobienne pourrait apparaître et se propager des déchets d'origine animale et des eaux usées d'origine humaine dans l'eau et le sol. Par conséquent le rôle de l'environnement dans la propagation de la résistance aux antimicrobiens doit être examinée plus avant.
- Le développement de plans d'action nationaux :
 - 18 Etats Membres de l'UE ont une stratégie nationale de lutte contre la résistance aux antimicrobiens, parmi lesquels 17 ont un plan d'action officiel.
 - Il n'y avait pas d'action spécifique ou de mécanismes d'appui lié au développement de plans d'action nationaux dans le plan d'action. Cependant les lignes directrices pour une utilisation prudente des

antimicrobiens en médecine vétérinaire publiées en 2015 appellent à la mise en place de stratégies holistiques et/ou de plans d'action.

Les domaines d'action de l'UE sont-ils appropriés en vue de la distribution des compétences entre l'UE et les Etats Membres ?

Un total de 84 pour cent des représentants d'Etats Membres ou de parties intéressées ayant répondu à l'enquête étaient d'accord ou tout-à-fait d'accord que le plan d'action de la Commission Européenne définissait des actions gérées au mieux au niveau de l'UE. L'UE a une plus large compétence politique en ce qui concerne les politiques liées à la santé animale qu'en ce qui concerne les politiques liées à la santé humaine. La responsabilité pour la recherche et l'innovation est une compétence partagée entre l'UE et les Etats Membres : les actions du plan d'action concernant la recherche et l'innovation se sont concentrées sur l'action de l'UE pour soutenir la recherche et assister les Etats Membres et les autres pays dans la coordination des programmes de recherche liés à la résistance aux antimicrobiens.

Efficacité

Dans quelle mesure les actions décrites dans le plan d'action ont-elles été efficaces pour améliorer le traitement des infections chez les humains et les animaux ?

La consommation d'antibiotiques chez les humains et les animaux

Le plan d'action a contribué à endiguer la consommation d'antimicrobiens par l'atteinte des objectifs politiques pour la santé humaine et animale. Les changements dans la consommation d'antimicrobiens chez les humains ou les animaux n'ont pu, cependant, être reliés au plan d'action, et ce pour deux raisons. Premièrement, au moment de l'évaluation, il était trop tôt pour observer et rendre compte des changements imputables au plan d'action. Deuxièmement, les effets du plan d'action ne pouvaient pas être discernés des effets d'autres initiatives politiques sur la résistance aux antimicrobiens mises en place antérieurement ou en parallèle du plan d'action. Un certain degré de variabilité a été observé entre les Etats Membres en termes de tendances de consommation de médicaments chez les humains et les animaux.

Au cours de la période de mise en œuvre du plan d'action, les politiques suivantes de traitement des infections chez les humains et les animaux ont été développées, mises en place et/ou évaluées :

- Les recommandations du Conseil (2002/77/EC and 2009/C 151/01) relatives à l'utilisation prudente des agents antimicrobiens en médecine humaine et à la sécurité des patients ont été évaluées. Les évaluations ont montré des améliorations quant à la mise en œuvre des exigences de prescription de médicaments uniquement sur ordonnance, à l'éducation et la formation sur la résistance aux antimicrobiens pour les professionnels de santé, et dans une moindre mesure la bonne gestion des antibiotiques et la mise en œuvre de mesures de contrôle contre la résistance aux antibiotiques dans les maisons de soins et les établissements de soins de longue durée. Les lignes directrices pour une utilisation prudente des antimicrobiens en santé humaine étaient développées au moment de l'évaluation.
- La Commission a introduit en 2015 des lignes directrices pour une utilisation prudente des antimicrobiens en médecine vétérinaire. La Commission a également adopté des propositions de règlement relatives aux médicaments vétérinaires et aux aliments médicamenteux pour animaux en 2014 (soumises à la procédure législative ordinaire au moment de l'évaluation). Les lignes directrices et les propositions législatives devraient promouvoir l'utilisation appropriée des antibiotiques vétérinaires.

- Les systèmes de suivi et de surveillance de l'UE au regard de la consommation d'antimicrobiens ont été renforcés. La couverture et l'étendue de la collection de données se sont améliorées à la fois pour le réseau de surveillance européen de la consommation d'antimicrobiens (ESAC), réseau des systèmes nationaux de surveillance sur la consommation d'antimicrobiens chez les humains, et pour le projet de surveillance européenne de la consommation d'antimicrobiens à usage vétérinaire (ESVAC), qui rassemble les données de vente d'antimicrobiens à usage vétérinaire.

La recherche et le développement

La recherche et le développement étaient des points majeurs du plan d'action et des progrès ont été faits dans ce domaine au niveau politique bien qu'il soit trop tôt pour évaluer l'impact et les résultats :

- Davantage de soutien pour la recherche sur la résistance aux antimicrobiens a été permis au travers des programmes cadres FP7 et Horizon 2020 ;
- La résistance aux antimicrobiens est devenue une des 12 priorités de l'initiative publique-privée sur les médicaments innovants (IMI) ;
- Le programme ND4BB a été lancé pour inciter au développement de nouvelles antibiotiques le long de la chaîne de valeur allant de la science fondamentale à de nouveaux modèles commerciaux et a créé les conditions pour le partage de données ouvertes ;
- Des améliorations dans la coordination entre pays ont été permis au travers de l'Initiative de Programmation Conjointe sur la résistance aux antimicrobiens (JPIAMR).

Dans quelle mesure les actions ayant pour but d'endiguer les risques de propagation de la résistance aux antimicrobiens ont-elles été efficaces?

Le plan d'action a contribué à l'endiguement des risques de propagation de la résistance aux antimicrobiens au travers de réussites politiques, notamment par une nouvelle législation. Cependant les changements dans la présence de résistance aux antimicrobiens chez les humains et les animaux ne pouvaient pas être liés au plan d'action pour deux raisons : i) au moment de l'évaluation, il était trop tôt pour que des changements imputables au plan d'action soient observés et rapportés ; et ii) les effets du plan d'action ne pouvaient pas être discernés des effets d'autres initiatives politiques liées à la résistance aux antimicrobiens mises en œuvre antérieurement ou en parallèle du plan d'action. Un certain degré de variabilité a été observé entre les Etats Membres en termes de tendances de résistance chez les humains et les animaux.

Au cours de la période de mise en œuvre du plan d'action, les politiques majeures suivantes concernant le risque de propagation de la résistance antimicrobienne ont été développées, mises en œuvre et/ou évaluées:

- La législation sur la santé animale a été adoptée par le Parlement Européen et le Conseil en Mars 2016. La loi introduit la base légale pour le suivi de la résistance aux antimicrobiens dans les pathogènes animaux et est vue comme une étape importante vers une meilleure prévention des infections.
- Les systèmes de suivi et de surveillance de l'UE ont été renforcés. La couverture et l'étendue des données collectées par le Réseau européen de surveillance de la résistance aux antimicrobiens (EARS-Net) se sont améliorées. Par ailleurs, la Décision 2013/652/EC concernant la surveillance et la présentation de rapports relatifs à la résistance aux antimicrobiens a étendu la couverture et le champ des données collectées sur les bactéries zoonotiques

et commensales chez les animaux producteurs d'aliments et certaines denrées alimentaires.

- La coopération internationale a été renforcée au travers d'initiatives soutenues par l'UE sur la résistance aux antimicrobiens, telles que la JPIAMR et le laboratoire de référence européen sur la résistance aux antibiotiques. L'UE a contribué au développement du plan d'action global de l'OMS, des standards du réseau mondial sur les infections d'origine alimentaire, des standards de l'organisation mondiale de la santé animale (OIE), du groupe de travail transatlantique sur la résistance antimicrobienne, des lignes directrices pour l'analyse des risques liés à la résistance aux antimicrobiens d'origine alimentaire (faisant partie du Codex Alimentarius), et au travail avec l'Organisation de coopération et de développement économiques (OCDE), la Chine et la Fédération de Russie.
- La communication a été renforcée au travers de la journée européenne de sensibilisation à l'usage des antibiotiques, qui a soutenu et encouragé le développement de campagnes nationales de sensibilisation à la résistance aux antimicrobiens, et a pu également contribuer à sensibiliser les décideurs politiques et les professionnels de santé. Néanmoins, une amélioration limitée a été observée quant à la connaissance du public de la résistance aux antimicrobiens à travers l'UE, comme étant mesurée par l'enquête Eurobaromètre.

Dans quelle mesure le champ d'application des mesures dans les différents services de la Commission Européenne a été efficace pour prendre en compte l'approche holistique et produire des résultats ?

Au total, 98 pour cent des personnes interrogées dans les enquêtes étaient d'accord avec le besoin d'adopter une approche holistique pour répondre au problème de la résistance aux antimicrobiens. Par ailleurs, 63 pour cent des personnes représentantes d'Etats Membres ou de parties intéressées ayant répondu à l'enquête estimaient que le plan d'action de la Commission Européenne adoptait cette approche holistique. De manière générale :

- Le plan d'action a été perçu comme étant holistique dans son contenu mais plus spécifiquement concentré sur certains secteurs dans sa mise en œuvre ;
- Le rôle de l'environnement dans la résistance aux antimicrobiens devrait être exploré plus avant ; et
- La mise en œuvre du plan d'action a impliqué une collaboration des Directions Générales et des agences mais cette collaboration a été moins visible pour les parties intéressées externes.

Efficiencia

Le budget de l'UE a-t-il été utilisé de manière efficace pour répondre aux objectifs du plan d'action ?

Des données limitées étaient disponibles sur les dépenses de l'UE pour les activités autres que la recherche, limitant sérieusement la possibilité d'évaluer l'efficacité du plan d'action. Les dépenses, spécifiquement de recherche, étaient alignées avec les objectifs du plan d'action et le soutien de l'UE a représenté une précieuse contribution au financement de la recherche sur la résistance aux antimicrobiens. Il n'a pas été possible d'évaluer l'impact et les résultats des activités de recherche et d'innovation en cours, car cela prend du temps avant que les efforts de recherche et développement produisent des résultats,

Cohérence

Dans quelle mesure le plan d'action est cohérent avec les stratégies nationales (ou régionales) et plans d'actions des Etats Membres et avec les initiatives similaires au niveau international ?

Le plan d'action est, dans une large mesure, cohérent avec les stratégies et actions plans des Etats Membres. Il a permis de galvaniser l'action des Etats Membres sur la résistance aux antimicrobiens et a influencé certains des plans d'action au niveau national, selon 56 pour cent des représentants d'Etats Membres ayant répondu au questionnaire. Par ailleurs, 61 pour cent ont indiqué que leur plan national et le plan d'action de la Commission Européenne avaient le même champ d'application, 26 pour cent ont répondu que le plan d'action de la Commission Européenne avait un champ d'application plus large et huit pour cent ont répondu que la politique nationale avait un champ d'application plus large, principalement au regard des aspects environnementaux.

La collaboration de l'UE avec des partenaires hors-UE dont les Etats-Unis, le Canada et la Norvège était alignée avec le plan d'action au travers du TATFAR (groupe de travail transatlantique sur la résistance antimicrobienne). De plus, le plan d'action de la Commission Européenne était, dans l'ensemble, cohérent avec le plan d'action global de l'OMS et avec le plan d'action de l'OMS pour la région européenne.

Dans quelle mesure les actions contenues dans le plan d'action sont-elles cohérentes avec les autres politiques européennes sur l'environnement, la santé humaine, la santé et le bien-être animal, la sécurité alimentaire, l'agriculture, la recherche, la compétitivité et les PME ?

Selon les représentants d'Etats Membres ou de parties intéressées ayant répondu à l'enquête, les politiques de l'UE sur la résistance aux antimicrobiens ont été complémentaires des politiques de l'UE existantes dans les domaines suivants : santé humaine (78 pour cent), santé et bien-être animal (80 pour cent), sécurité alimentaire (75 pour cent) et recherche (77 pour cent).

Concernant l'environnement, seulement 56 pour cent des personnes interrogées étaient d'accord ou tout-à-fait d'accord que la politique de l'UE sur la résistance aux antimicrobiens a complété ou renforcé la politique de l'UE sur l'environnement. Tandis que le plan d'action n'était pas inconsistant avec la politique de l'UE sur l'environnement, il aurait pu être plus cohérent si l'ampleur de sa couverture des aspects environnementaux avait inclus un plus large éventail de sujets, notamment les impacts des déchets agricoles et humains sur la transmission de la résistance aux antimicrobiens.

Valeur ajoutée

Quelle est la valeur ajoutée résultant du plan d'action de la Commission Européenne en comparaison avec ce qui aurait pu être atteint par les Etats Membres aux niveaux national et régional? Le plan d'action a-t-il identifié des actions qui seraient mieux gérées au niveau européen ?

Dans l'ensemble, 84 pour cent des représentants d'Etats Membres ou de parties intéressées ayant répondu à l'enquête étaient d'accord ou tout-à-fait d'accord que le plan d'action a identifié les actions pouvant être gérées au mieux au niveau de l'UE. Le plan d'action a apporté une valeur ajoutée dans la lutte contre la résistance aux antimicrobiens de deux importantes manières :

- Le plan d'action a agi comme un symbole de l'engagement politique de l'UE et a stimulé l'action aux niveaux européen et mondial.
- Le plan d'action a fourni une structure pour guider et coordonner les activités nationales sur la résistance aux antimicrobiens, permettant à ces activités d'être plus efficaces qu'elles ne l'auraient été autrement. Les domaines ayant

clairement bénéficié de l'amélioration de la coordination internationale ont été ceux de la recherche et l'innovation et du suivi et de la surveillance.

Dans quelle mesure les améliorations de la situation au regard de la résistance aux antimicrobiens (résultats et autres changements identifiés dans les questions d'évaluation précédentes) sont-elles associées avec le développement et la mise en œuvre du plan d'action de la Commission Européenne ?

Les représentants d'Etats Membres ou de parties intéressées ayant répondu à l'enquête étaient d'accord ou tout-à-fait d'accord (78 pour cent) que le plan d'action de la Commission Européenne a contribué à apporter des améliorations de la situation au regard de la résistance aux antimicrobiens qui n'auraient pas pu être possibles autrement. Les progrès ont inclus :

- Le développement de nouvelles politiques et directives de l'UE, dont la nouvelle législation sur la santé animale, les lignes directrices pour une utilisation prudente des antimicrobiens en médecine vétérinaire et les propositions de règlement relatives aux médicaments vétérinaires et aux aliments médicamenteux pour animaux, et le développement de lignes directrices pour l'utilisation prudente en médecine humaine.
- Un accroissement de la conscience mondiale par rapport à la résistance aux antimicrobiens et la contribution aux efforts de coordination internationale par rapport à la R&D et le suivi et la surveillance.
- L'harmonisation, l'intégration, l'amélioration de la qualité et une meilleure couverture des données de suivi et de surveillance sur la consommation d'antibiotiques et la résistance à travers l'UE.
- L'organisation de campagnes de sensibilisation nationales dans certains des Etats Membres, encouragées par la journée européenne de sensibilisation à l'usage des antibiotiques, une initiative datant d'avant le plan d'action puis continuée sous le plan d'action.
- Le financement européen pour les projets de R&D liés à la résistance aux antimicrobiens, qui a augmenté sous le plan d'action. En termes de dépenses mondiales en R&D liée à la résistance aux antimicrobiens, les fonds européens ont représenté une source considérable de financement public.

Recommandations

La résistance aux antimicrobiens reste un problème urgent dans l'UE et internationalement. Le plan d'action a contribué à galvaniser l'action sur les questions liées à la résistance aux antimicrobiens au sein de l'UE et a encouragé l'engagement avec des pays tiers et la communauté internationale pour lutter contre la résistance aux antimicrobiens. L'UE devrait mettre à profit les progrès accomplis et continuer à jouer un rôle actif dans ce domaine, conformément avec les recommandations suivantes :

1. Un soutien coordonné additionnel devrait être fourni aux Etats Membres.

La consommation d'antimicrobiens et les niveaux de résistance sont extrêmement variables entre les Etats Membres. Par conséquent, une approche unique pour résoudre ce problème est insuffisante. Un soutien à la fois financier et technique sera probablement requis, particulièrement pour les pays en retard. L'action future de l'UE pourrait inclure un mécanisme pour encourager et soutenir les Etats Membres dans le développement et la mise en œuvre des plans d'action nationaux.

2. La portée de l'action environnementale devrait être étendue.

Il est nécessaire d'améliorer la compréhension du rôle de l'environnement dans l'émergence et la transmission de la résistance au travers des déchets d'origine animale, humaine et d'usinage dans l'eau et le sol, et d'examiner quelles actions peuvent être requises afin de réduire les risques associés. La Direction Générale pour l'Environnement (DG ENV) devrait contribuer à la conception et la mise en œuvre de futures actions dans ce domaine.

3. L'UE devrait contribuer encore davantage aux efforts internationaux.

Etant donné l'importance accrue de la dimension internationale de la résistance aux antimicrobiens, l'UE devrait renforcer les activités de coopération internationales liées au développement de systèmes de surveillance mondiaux. Ceci contribuerait à répondre aux défis associés à la migration, au tourisme et au commerce qui s'accompagnent d'un potentiel de propagation croissant de la résistance aux antimicrobiens dans l'UE et au-delà.

4. L'UE devrait maintenir son appui aux activités de recherche et d'innovation.

Les activités de recherche et d'innovation liées à la résistance aux antimicrobiens sont un domaine dans lequel l'UE a joué un rôle important au niveau mondial. Un financement primordial, étendu aux activités de recherche, a été initié par le plan d'action. L'UE devrait maintenir son soutien pour les projets et programmes qui ont été commencés.

En collaboration avec l'initiative de programmation conjointe sur la résistance aux antimicrobiens (JPIAMR), la Commission devrait également examiner les sujets devant être couverts par le financement européen, en particulier la recherche liée aux diagnostics, vaccins, alternatives aux antimicrobiens pour le traitement des infections ainsi qu'aux facteurs sociaux et comportementaux qui motivent l'utilisation d'antimicrobiens et l'interaction entre l'environnement et la résistance aux antimicrobiens.

5. L'UE pourrait étendre son suivi de la résistance aux antimicrobiens et des activités liées à la résistance aux antimicrobiens.

Les améliorations dans le suivi et la surveillance de la résistance aux antimicrobiens et de l'utilisation des antimicrobiens ont été des succès majeurs du plan d'action. L'enquête Eurobaromètre a également fourni une source importante de données sur la sensibilisation du public à la résistance aux antimicrobiens dans l'UE. La disponibilité limitée des données sur les dépenses a affecté la transparence sur les coûts associés à la résorption de la résistance aux antimicrobiens au sein de l'UE. Des mesures peuvent être prises dans chacun de ces domaines :

- L'UE devrait continuer à soutenir un système plus holistique pour le suivi des questions de résistance aux antimicrobiens : relier les données sur la résistance, la consommation et les ventes d'antimicrobiens aux tendances de prescriptions et autres facteurs en santé humaine et animale – et potentiellement l'étendre à l'environnement. Un tel système fournirait une image plus complète de la situation de la résistance aux antimicrobiens et aiderait à identifier les zones problématiques.
- Des objectifs et indicateurs associés pourraient être introduits, notamment et selon le cas, des objectifs et indicateurs par pays pour s'assurer que des informations sont collectées sur l'évolution des questions liées à la résistance aux antimicrobiens par rapport aux activités et résultats de court-terme, afin d'aider à évaluer les progrès et les relier aux résultats et impacts de long-terme. Des objectifs liés à des indicateurs de long-terme, tels que l'utilisation

des antimicrobiens ou la présence de résistance pourraient également être considérés.

- Contrôler le rapport coût-efficacité afin de s'assurer que les investissements financiers adéquats sont fait pour appuyer les mesures visant à combattre la résistance aux antimicrobiens mondialement.
 - Le suivi de la sensibilisation du public à la résistance aux antimicrobiens devrait continuer; l'UE devrait continuer à soutenir les activités de sensibilisation au travers de la journée européenne de sensibilisation à l'usage des antibiotiques.
6. Les institutions et agences de l'UE pourraient mieux communiquer sur leurs efforts auprès des parties intéressées et du grand public.

Le plan d'action a rassemblé avec succès les actions liées à la santé et au bien-être animal, la sécurité alimentaire et la santé humaine dans un même instrument politique conforme avec l'approche 'One Health'. La Commission et ses agences ont collaboré à l'échelle de différentes Directions Générales et agences pour mettre en œuvre le plan d'action. Tandis que certaines activités collaboratives étaient très visibles, telles que les rapports inter-agences, les parties intéressées externes étaient moins conscientes de la collaboration mise en œuvre au sein de la Commission. Par conséquent :

- La Commission pourrait mieux communiquer afin d'accroître la connaissance de leur travaux et autres activités intersectoriels, et leur relation avec le plan d'action. Une telle communication permettrait aux autres pays et organisations d'apprendre de l'approche adoptée par l'UE.
- Cette approche collaborative pourrait également s'étendre pour concerner les interactions entre les parties intéressées représentants les différents secteurs impliqués dans la lutte contre la résistance aux antimicrobiens mais n'interagissant pas traditionnellement.

1. INTRODUCTION

1.1 Background to the study

This is the final report for an evaluation of the European Commission's 'Communication to the European Parliament and the Council Action Plan against the Rising Threats from Antimicrobial Resistance' (COM(2011) 748) (hereafter, the Action Plan).¹ The Action Plan (2011-2016) is a policy instrument to address the problem of antimicrobial resistance (AMR) at European level across the following areas: monitoring and surveillance; appropriate use of antimicrobials; infection prevention; development of new antimicrobials, alternative treatments and development of diagnostic tools; improving understanding of AMR; and reinforcement and coordination of research efforts (EC 2011). The objectives also covered international cooperation and awareness, education and training. The plan was designed to take a holistic approach across multiple sectors, covering human and veterinary aspects to protect both human and animal health. The EC Action Plan on AMR was published in 2011 and covered a five-year period, through 2016.

This evaluation was commissioned by the Directorate-General for Health and Food Safety (DG SANTE) in September 2015. The evaluation was delivered by RAND Europe, working with a team of experts on AMR covering both the human and animal health aspects of the issue.

The final report presents the findings, conclusions and recommendations for the evaluation, incorporating information obtained by the study team through consultation and desk research. An overview of the available information contributing to this report is provided in Section 2.

This section sets out the evaluation context by briefly describing the AMR challenge, summarising European Union (EU) action on this issue, and concluding with the Action Plan as the subject of this evaluation.

1.1.1. Summary of the issue

Starting with the commercialisation of penicillin in the 1940s as an agent for treating bacterial infections, antimicrobials have transformed medicine. Antimicrobial agents — including antibiotics, antifungals and antivirals — made it possible to treat deadly infections, such as tuberculosis (TB), and to reduce the risk of complications associated with surgery, organ transplantation, joint replacements and cancer chemotherapy. AMR is a naturally occurring phenomenon, but the use of antimicrobials has also led to antimicrobial resistance, where micro-organisms evolve abilities to survive drugs intended to kill them or stop their growth (Davies et al. 2013). AMR has been an issue since antibiotics were introduced, but the challenges it brings are now compounded by an increase in resistance and a lack of new antimicrobial agents being developed (Chief Medical Officer 2011). Experts have warned that if AMR is not addressed, there is a risk that modern medicine will be undermined: common medical procedures will become unviable and mild infections will become extremely serious (O'Neill Review 2014; ECDC & EMEA 2009).

Recognition has grown about the risks of AMR as the tools relied on in both human and veterinary medicine to treat dangerous infections become increasingly ineffective. The World Health Organization (WHO) (2012) has called upon the international

¹ Contract reference SANTE/2015/G4/SI2.712688, implementing framework contract No SANTE/2012/02/011 — Lot 1 and Lot 3.

community over the past two decades to take measures to reduce the spread of AMR. The 2013 World Economic Forum identified AMR as one of the greatest risks to human health. AMR is a global challenge, threatening both high-income and poorer countries and exacerbated by international trade and travel, which enable the spread of drug-resistant organisms.

1.1.2. The AMR challenge

AMR can pass between animal and human populations, and it can spread in the environment. As a result, tackling AMR requires a broad approach that addresses the use of antimicrobials in veterinary medicine (both in livestock and in pets); in human medicine; and in environments where resistant bacteria can accumulate, such as wastewater systems (POST 2013).

This has led to adoption of the 'one Health' approach, which, while lacking a precise definition (Bonk 2015), brings together animal health, human health and the environment as interconnected areas that are important for addressing AMR (Torren-Edo et al. 2015). Addressing these areas together requires collaboration by multiple actors: veterinarians, clinicians and others. The 'one health' approach has been promoted by the EU since 2008 (EEAS 2015).

Action is needed to join up international efforts in tackling and monitoring AMR, which complement actions that address the use of existing antimicrobials and the spread of drug-resistant organisms. There is also a need to raise awareness about the risks of AMR and what all stakeholders — including the general public and medical and veterinary professionals — can do to mitigate AMR risks (WHO 2012).

A particular challenge for dealing with AMR relates to the lack of new antibiotics being developed, particularly since the 1970s (ECDC & EMEA 2009). Innovation in antimicrobials, diagnostics and vaccines has not kept pace with the need for improved treatment options (WHO 2012). As a result, there is a gap between the AMR burden, particularly with regards to multi-drug-resistant organisms, and the development of new antimicrobials (ECDC & EMEA 2009).

1.1.3. EU action on AMR

This section summarises EU action on AMR since 2001.

1.1.3.1. EU efforts to tackle AMR: 2001-2010

Efforts to tackle AMR at the EU level predate the Action Plan (COM(2011) 748). In 2001, the Community strategy against AMR in human medicine (COM(2001) 333) (EC 2001) laid the foundations for EU actions in the fields of surveillance, research, prevention and international cooperation. The strategy led to the adoption of EU-wide recommendations and guidelines, for example, the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine, developed with the contribution of the WHO, and the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections.

In human medicine, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use is aimed at removing the barriers to the free movement of medicinal products within the EU. In veterinary medicine, specific measures were taken to monitor zoonotic² AMR and the use of antimicrobials in animals. Member States were mandated to, inter alia, monitor and report comparable data on AMR in zoonotic

² Transmissible between animals and humans.

agents.³ Detailed monitoring rules were adopted in 2007.⁴ The Commission also banned the use of antimicrobials as feed additives in animal farming for growth promotion, which came into effect in 2006,⁵ and specific legislation was developed to control *Salmonella* in animals, namely, Commission Regulation (EC) No 1168/2006 of 31 July 2006 implementing Regulation (EC) No 2160/2003 as regards a Community target for the reduction of the prevalence of certain salmonella serotypes in laying hens of *Gallus gallus*⁶ and Commission Regulation (EC) No 1177/2006 of 1 August 2006 implementing Regulation (EC) No 2160/2003 of the European Parliament and of the Council as regards requirements for the use of specific control methods in the framework of the national programmes for the control of salmonella in poultry.

1.1.3.2. The EU AMR Action Plan: 2011-2016

The focus of this evaluation was the 'Action Plan against the Rising Threats from Antimicrobial Resistance' (COM(2011) 748) (EC 2011). The Action Plan brought together interested parties from across Europe to identify objectives and related measures to be implemented by 2016 to address AMR issues. The Action Plan was developed on the basis of scientific opinions on AMR from EU risk assessment bodies, including the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), the European Medicines Agency (EMA) and the SCENIHR.

The Action Plan had seven core objectives. The objectives emphasised the appropriate use of antimicrobials and infection prevention, the development of alternative or effective treatments and diagnostics, improving understanding of AMR, and the reinforcement and coordination of research efforts. The objectives covered the improvement of monitoring and surveillance related to AMR. Objectives also included use of antimicrobials, strengthening international cooperation and improving awareness and education. The Action Plan set out 12 actions in human and veterinary medicine to achieve these objectives (Figure 1).

³ On the basis of Directive 2003/99/EC of the European Parliament and of the Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents, amending Council Decision 90/424/EEC and repealing Council Directive 92/117/EEC.

⁴ Commission Decision of 12 June 2007 on a harmonised monitoring of antimicrobial resistance in *Salmonella* in poultry and pigs (2007/407/EC).

⁵ Regulation (EC) No 1831/2003 of the European Parliament and the Council of 22 September 2003 on additives for use in animal nutrition, replacing Directive 70/524/EEC on additives in feeding-stuffs.

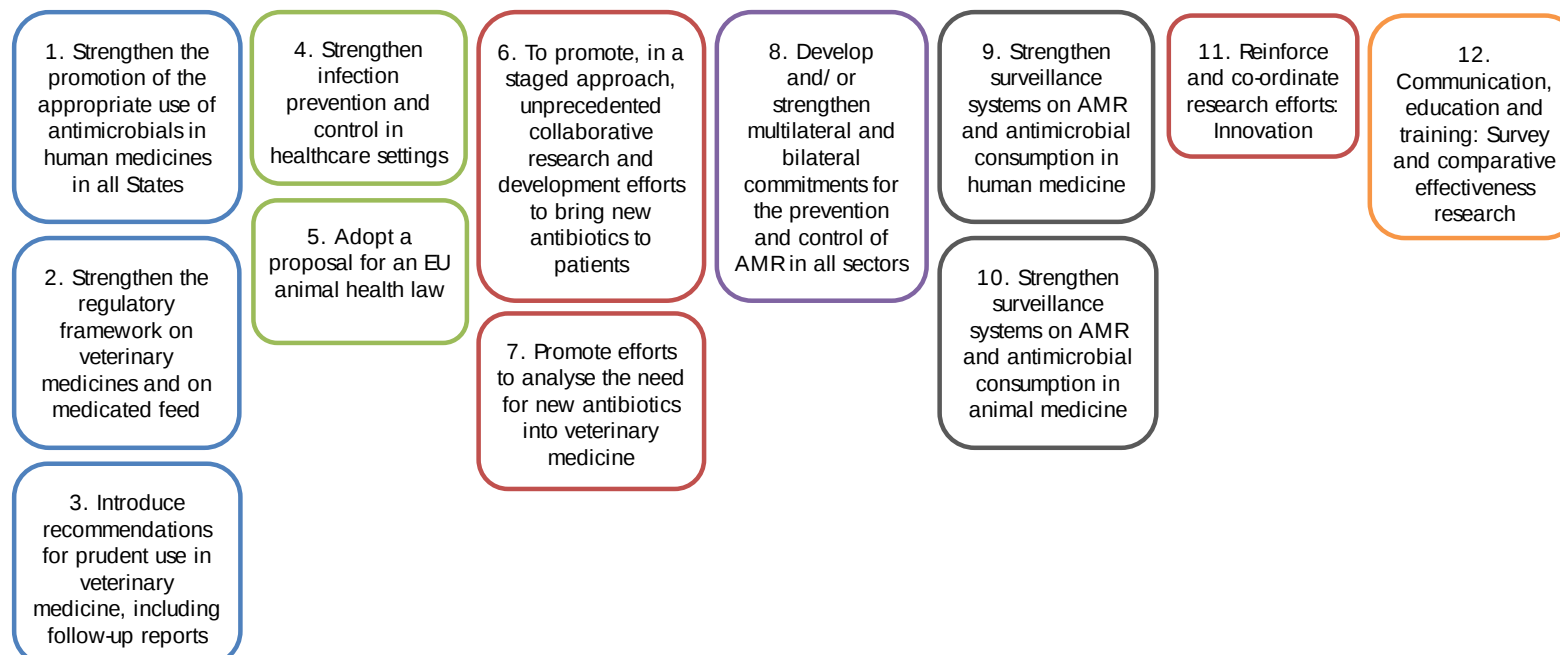
⁶ And amending Regulation (EC) No 1003/2005.

Figure 1: Core objectives of the EC Action Plan on AMR and associated strategic actions

Core objectives



Strategic actions



Source: RAND Europe.

The Action Plan promoted taking a holistic approach to the threat of AMR. It acknowledged that actions taken up to 2011 had not contained the threat and that future actions needed to involve a wider share of stakeholders across the impacted sectors in human medicine, veterinary medicine, research, animal husbandry, agriculture, environment and trade.

Furthermore, the Action Plan focused on strengthening existing surveillance networks and data on the consumption of antimicrobial agents for human and animal medicine. The Action Plan reinforced existing actions by insisting on supporting collaborative research projects and promoting the launch of a Joint Programming Initiative (JPI) to coordinate national research activities. It aimed to establish a large-scale public-private collaboration specifically focused on antimicrobial research and development. It also aimed to strengthen education campaigns, for example, through European Antibiotic Awareness Day (EAAD), and involved a new, EU-wide survey to assess the impact of awareness campaigns and improve their effectiveness.

1.2 Study objectives and scope

The purpose of this evaluation was to assess the impact of the implementation of the Action Plan (see Evaluation Terms of Reference, Appendix A). More specifically, the objectives of this evaluation were to analyse whether the 12 strategic actions contained in the Action Plan were the most appropriate actions to be taken to combat AMR and which elements worked well or not (and why). The objectives also included assessing whether the objectives of the Action Plan were still relevant to current needs in tackling AMR and whether the approach was appropriately holistic.

The evaluation covered the period 2011-2015. The scope of the evaluation included all of the strategic actions and core objectives set out in the Action Plan and assessed activities undertaken in relation to the Action Plan in all Member States and for all stakeholder groups involved in its implementation. In addition to assessing the impact of the Action Plan, the evaluation also identified areas where actions could be improved in the future.

The evaluation followed the Commission's guidelines on better regulation in SWD [staff working document] (2015) 111 (EC 2015e) and the associated *Better Regulation "Toolbox"*. It focused on five evaluation criteria: relevance, effectiveness, efficiency, internal and external coherence, and EU added value. The terms of reference set out 10 evaluation questions to be addressed in this study corresponding with the evaluation criteria. The questions and corresponding evaluation criteria are provided in Table 1.

Table 1: Evaluation criteria and related evaluation questions

Criterion	Evaluation question (EQ)	
Relevance	EQ1	To what extent do the objectives of the Action Plan address the problems identified in 2011? How well do these objectives still correspond to the current needs of tackling AMR within the EU?
	EQ2	Are the areas for EU action appropriate in view of the distribution of EU and national competences?
Effectiveness	EQ3	To what extent have the actions been effective at <i>improving treatment</i> of infections in humans and animals?
	EQ4	To what extent have the actions aimed at <i>containing the risks of spreading AMR</i> been effective?
	EQ5	To what extent has the European Commission been effective in capturing the holistic approach and delivering results?
Efficiency	EQ6	Has the EU budget been efficiently used to address the objectives of the Action Plan?
Coherence	EQ7	To what extent is the Action Plan coherent with Member States' relevant national (or regional) strategies and action plans and with similar initiatives at the international level?
	EQ8	To what extent are the actions contained in the Action Plan coherent with other EU policies on the environment, human health, animal health and welfare, food safety, agriculture, research, competitiveness and SMEs?
EU added value	EQ9	What is the added value resulting from the EC Action Plan compared with what could be achieved by Member States at national and/or regional levels? Did the EC Action Plan identify the actions which should be best dealt with at EU level?
	EQ10	To what extent can improvements in the situation on AMR (outcomes and other changes identified in the previous EQs) be attributed to the development and implementation of the EC Action Plan?

1.3 Purpose and structure of the report

The final report presents the approach and method for the evaluation; analysis of each evaluation question; conclusions; and, where relevant, recommendations. Each chapter is dedicated to a specific evaluation criterion and its related evaluation questions. A set of appendices (provided as a separate document) contain supporting materials, including data underlying the research results and analysis to support the findings presented in the main report.

2. SUMMARY OF THE EVALUATION APPROACH AND METHODS

This section describes the approach and method for the evaluation in brief. A detailed description is provided in Appendix B. The overall approach to the evaluation was a multi-method study to identify quantitative and qualitative findings across the actions. An intervention logic (Appendix C) and evaluation matrix (Appendix D) were developed, presenting judgement criteria and indicators covering each evaluation question. Data sources were identified for each indicator, which required the collection of primary quantitative and qualitative information and the review of secondary data. A stakeholder mapping exercise was undertaken to ensure that all relevant stakeholders were consulted for the evaluation (Appendix E).

2.1 Primary data collection

Primary data collection included workshops, public consultation, a Member State survey, a stakeholder survey and in-depth interviews. A summary of the data collection methods and the targeted and actual number of participants for each method is provided in Table 2.

2.1.1. Stakeholder workshops

Two stakeholder workshops were conducted as part of the evaluation. The first workshop, held on 26 October 2015, was designed to inform stakeholders about the evaluation, explain how they could be involved, and generate interest in further participation. The workshop also obtained evidence from stakeholders regarding observed changes in AMR-related issues and the Action Plan. The second workshop, held on 16 February 2016, served as an opportunity to discuss the evaluation outcomes for the purpose of validating the findings and recommendations.

Details of the workshops, including the format and structure, are provided in Appendices F and G. The findings were summarised in reports that were circulated to participants for their comment and validation following each workshop (Appendix H).

Table 2: Data collection methods and participation

Method	Purpose	Target no. of participants	Actual no. of participants
Workshop 1	Inform stakeholders about the evaluation and obtain evaluation evidence	25	29 (representing 23 organisations)
Public consultation	Gather evidence from any member of the public who wishes to participate	n/a	34**
Member State survey	Gather evidence from Member State representatives on animal and public health issues and the role of the Action Plan	56*	70** (representing 26 Member States, Iceland, Norway, Serbia and Switzerland)
Stakeholder survey	Gather evidence from targeted stakeholders on animal and human health issues and the role of the Action Plan	50	81**
Interviews	Gather qualitative information to complement the surveys and other data collection methods	25	38
Workshop 2	Discuss and validate evaluation outcomes	25	38 (representing 36 organisations)

* The target represents the potential number of Member State respondents on each issue (assuming at least one respondent each representing human and animal health issues from each of the 28 Member States). Some Member States provided a single, coordinated response in each area (human and animal health), while others provided two or more responses.

** A total of 64 responses were received as part of the public consultation, of which 34 were from self-identified members of the public (of these, 2 were emailed responses that did not answer the questions in the questionnaire); 3 were Member State responses routed to the targeted Member State survey; and 27 were stakeholder responses routed to the targeted stakeholder survey.

2.1.2. Public consultation

A 12-week online open consultation in English was held from 30 October 2015 to 22 January 2016. The consultation was hosted by the Commission through its 'Your voice in Europe' website.⁷ A questionnaire was used, which covered all mandatory evaluation criteria (relevance, effectiveness, efficiency, coherence and added value) in accordance with EU public consultation guidelines (EC 2015a). The consultation gathered views and opinions from any member of the public who wished to participate. A total of 64 submissions were received; 34 responses were received from self-identified members of the public, of which 32 responded to the consultation questionnaire and were analysed. Participants who self-identified as experts in AMR issues were routed to the targeted surveys for stakeholders (27 responses) or Member State representatives (3 responses) (see Sections 2.1.3 and 2.1.4). Introductory information, the privacy statement and questions are provided in Appendices I and J. A synopsis report of the results from the consultation is provided in Appendix L.

⁷ http://ec.europa.eu/yourvoice/consultations/index_en.htm

2.1.3. Targeted surveys

Two versions of a survey targeting public sector representatives in the EU-28 Member States were designed: one to cover issues specific to human health and one for animal health. Furthermore, two versions of a survey targeting stakeholders on AMR issues were also designed, mirroring the Member State surveys covering issues specific to human and animal health. The surveys were hosted online in English and ran for nine weeks.⁸ The questions are provided in Appendix J.

The groups represented in the Member State survey and the number of responses by affiliation are provided in Table 3. Representatives from 26 Member States, Iceland, Norway, Switzerland and Serbia replied to the survey.

Table 3: Member State representatives – Survey responses

Affiliation	No. of responses*
Government ministry	25
Public health authority	25
Food safety authority	22
Veterinary authority	25
Research organisation	7
ECDC Coordinating Competent Body	7
EARS-Net national participating institution	12
EMA National Competent Authority	9
EFSA Focal Point	2
Other institution involved in AMR strategies	7

* The total number of respondents was 70. Some respondents had more than one affiliation.

The stakeholder groups targeted for the survey included those with whose members have experience in areas related to animal health, farming and food, human health, and research and innovation. The groups represented in the stakeholder survey and the number of responses by affiliation are provided in Table 4.

Table 4: Stakeholder representatives – Survey responses

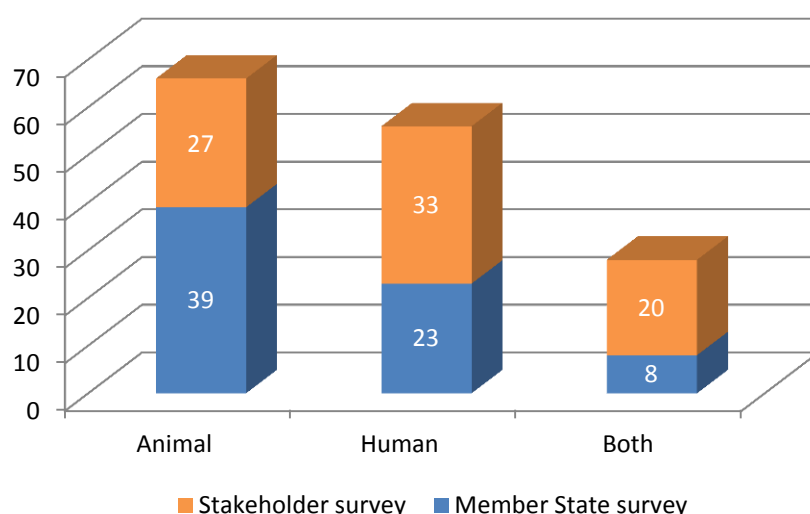
Affiliation	No. of responses*
NGO	19
Industrial or trade association	17
Healthcare, hospital, health institution	10
Academic or research centre	8
Private company	6
Consultancy	2
'Other' or not indicated	19

* The total number of respondents was 81.

A total of 151 survey responses were received across both groups. Respondents were asked to identify whether they were responding as an expert in human health, animal health or both (Figure 2). Human health respondents represented 44 % of responses and animal health experts represented 37 %; 19 % indicated that they had expertise in both areas and one respondent was unsure.

⁸ Due to difficulties in obtaining contact details for some representatives, some representatives/national contact points for the following agencies had a shorter timeframe to complete the study: EMA veterinary authorities (seven weeks), EMA human health authorities (six weeks), and EFSA (five weeks).

Figure 2: Total number of survey respondents who self-identified as an expert in human health, animal health or both



Source: Targeted evaluation surveys, 2016.

2.1.4. Interviews

In-depth interviews were conducted to collect qualitative information to complement the survey data. Interviews targeted representatives of the European Commission and relevant DGs; EU agencies, such as the ECDC, EFSA, and EMA; non-governmental and international organisations; and EU-level interest groups. Interviews also targeted recipients of EU research funds. Interviews were conducted by telephone, in English. The interview protocols are provided in Appendix K. The number of interviews conducted by affiliation group, as well as the number of interviews conducted for the case studies, are provided in Table 5.

Table 5: Interviewee affiliation and number of interviews conducted by affiliation group

Affiliation	No. of interviews*
European-level policy and public body representative, third-country expert	11
International body	4
Research and innovation stakeholder	8
Independent expert on AMR issues	2
<i>Various (case study interviews)</i>	13

* The total number of interviews conducted was 38.

2.2 Secondary data analysis and synthesis

2.2.1. Desk research

Desk research was undertaken to collect data and information to design the consultation tools (such as interview protocols and surveys) and to answer the evaluation questions. A non-exhaustive list of the literature consulted for this study is provided in the references list at the end of this report. The types of sources consulted include legislative documents, scientific guidelines, surveillance reports, surveillance data relating to animal and human health, public surveys, stakeholder reports and academic literature. The secondary data and information used in the evaluation differed by evaluation question. The evaluation matrix, presented in Appendix D,

identifies the indicators that rely on secondary information and the main sources of this information.

2.2.2. Case studies

Eight case studies were conducted, focusing on AMR-related issues in specific countries. The objective of the case studies was to test assumptions about the impacts of the Action Plan, including similarities and differences in countries' approaches to the tackling AMR, and the link between actions on AMR issues and the role of the Action Plan. Case studies involved desk research and interviews. The case study topics were:

1. **Healthcare-associated infections:** understanding progress at EU and country level, focusing on the Netherlands and Portugal;
2. **Multidrug and extensively drug-resistant TB:** progress and challenges in eastern European countries in the EU;
3. **Treat Antibiotics Responsibly, Guidance, Education, Tools (TARGET) antibiotics toolkit** for antimicrobial stewardship;
4. **ESVAC data:** successes and future directions;
5. **Salmonella prevalence in the EU:** effect of the Action Plan across animal health, human health and food safety;
6. **French awareness programmes:** lessons learnt on human health with extension to animals;
7. **Aquaculture** and AMR in maritime waters; and
8. **Trends in community antibiotic use and public awareness:** Italy and Sweden.

A description of the case studies and related evaluation questions is provided in Appendix B. The complete set of case study reports is provided in Appendix N.

2.2.3. Final synthesis and triangulation

Primary and secondary data were brought together through synthesis of the evidence by indicator, aggregated up to judgement criteria and assessed as a whole in relation to each evaluation question. Triangulation was three-fold. First, we ensured that different data sources aligned or that their differences were explained. Second, we brought together and standardised the presentation of information by different researchers. And, third, because the available data came from different sources, we took this into account in the preparation of the findings and conclusions, for example, by considering the relative weight of evidence from different sources.

2.3 Validity and limitations

This section presents issues related to the study's validity and limitations, as well as efforts taken by the study team to address or redress these in the evaluation.

2.3.1. Scope of the evaluation in relation to the time and resources available

The evaluation scope was very broad, encompassing human and animal health issues and covering upstream scientific research (e.g. drug development) through to consumer awareness. Geographically, the study covered the EU-28 Member States and some third countries, namely, Norway, Switzerland, Iceland, Serbia, the United States, Canada, China and Russia. The approach selected was by necessity pragmatic in terms of possible data sources and the issues that could be covered. The evaluation addressed all of the required evaluation criteria and questions, but the depth and

breadth of coverage of each varied in light of data availability and accessibility (Section 2.3.4), as well as time and resource constraints on undertaking the evaluation.

2.3.2. Attribution

Attributing changes to the Action Plan that were not directly related to specific actions (e.g. the development of guidelines) was challenging because there were many initiatives and interventions taking place related to AMR at the national, regional and international levels. Given the multitude of AMR activities, the role of one specific initiative, such as the Action Plan, should not be overstated. Additionally, some activities, such as the establishment of national guidelines on prudent use of antimicrobials in medicine, had begun prior to the Action Plan, although they may have improved or intensified following its publication.

It was therefore possible that some of the Member State activities to which the Action Plan was found to have contributed would have occurred even without the existence of the Action Plan. That possibility was suggested by some survey respondents and interviewees, who observed that several of the actions included in the Action Plan were ongoing in at least some Member States before the Action Plan began, in some cases even to a greater degree than called for by the Action Plan. This possibility makes it inherently problematic to assess the 'unique' contribution of the Action Plan.

There was also uncertainty surrounding the extent to which the EU was going to take action in the areas covered by the Action Plan even if the Action Plan had not been adopted, for example, through bilateral and multilateral commitments. Some of the developments presented in this report represent a continuation of already existing efforts, albeit in some instances in an intensified approach. It is possible that the EU would have pursued these efforts even without an Action Plan, because the 'strengthening' or 'deepening' of existing cooperation mechanisms can be seen as a desirable objective irrespective of its formalisation in an Action Plan.

Survey questions were formulated to ask whether (and to what extent) changes could be attributed to the Action Plan, since survey respondents were unlikely to attribute a change entirely to the Action Plan. Nevertheless, attribution challenges resulted in many respondents being unsure or answering that they did not know whether the Action Plan played a role across many of the areas evaluated in this study.

Throughout the report, the study team was mindful of these challenges related to attribution. The findings for each evaluation question are presented according to the strength of evidence. Caveats are made explicit in the presentation of findings, and conclusions are tempered so that claims of attribution or the impact of the Action Plan are appropriate given the available data.

2.3.3. Timeframe

Another issue for the evaluation was the timing of the analysis in the lifecycle of the Action Plan and its activities. Identifying impact was impossible for a number of the initiatives, particularly in the area of research and development for new antimicrobials, which could not be expected to have produced significant results at this stage. The difficulty presented by delayed impact was exacerbated by the fact that several initiatives, such as the guidelines on prudent use of antimicrobials in animals, published in September 2015, were in their infancy as regards implementation. Others, such as the Commission proposals for revised legislation on veterinary medicines and medicated feed, were not in force. Reliable data on the long-term outcomes and impacts of these activities were unavailable. In these cases, the study team focused on short-term outcomes and also on outputs and activities related to specific actions in order to assess success at this stage. Even where data were available, for example, with respect to trends in use of antimicrobials, it was too early to see whether there were any significant changes arising from the Action Plan.

2.3.4. Data availability and accessibility

Data availability was an issue for the study. For example, most financial information from EU agencies was not disaggregated to a level which identified it as specifically associated with AMR. In other areas, such as healthcare-associated infections (HAIs), improvements were made to standardise measurement and carry out a point prevalence survey (PPS) at EU level, but time series data were not available.

It was necessary to rely primarily on consultation results for some evaluation questions, and in a few cases, mostly on interviews with individuals involved in developing and implementing AMR policies and addressing AMR, because other forms of documentation did not provide information that was directly relevant to the evaluation questions. Those who were most familiar with the Action Plan and best placed to provide concrete information about its value were those who were directly involved in its implementation, such as Commission representatives. An effort has been made to triangulate and validate their statements with other sources of information where possible, but it remained a challenge for some evaluation questions.

Finally, a public consultation was conducted on the 'Your Voice in Europe' website, which was intended to reach stakeholders who may not have been reached through the targeted surveys, as well as interested members of the general public. The consultation was able to capture additional expert views on the Action Plan (27 stakeholders and 3 Member State representatives), and these survey responses were included in the targeted survey responses reported in this evaluation report. The response from the general public was very low (34), although the findings from questions that mirror questions posed to stakeholders and Member State representatives were similar.

2.3.5. Defining the 'holistic approach'

There is no precise or agreed upon definition of what it means to have a 'holistic approach' in the context of AMR. Consequently, determining whether the approach was appropriately holistic was based on whether there was evidence indicating that important sectors were neglected in the Action Plan. Assessing definitively whether the holistic approach was effective in delivering results was not possible in the absence of evidence from a counterfactual scenario; however, it was possible to seek information in surveys about how the Action Plan could have been made more holistic and to explore in interviews what was achieved through inclusion of the 'one health' concept in the Action Plan.

3. RELEVANCE — FINDINGS AND CONCLUSIONS

This section reports the findings and conclusions on evaluation questions related to the relevance of the EC Action Plan.

3.1 Extent to which objectives address problems identified in 2011 and currently

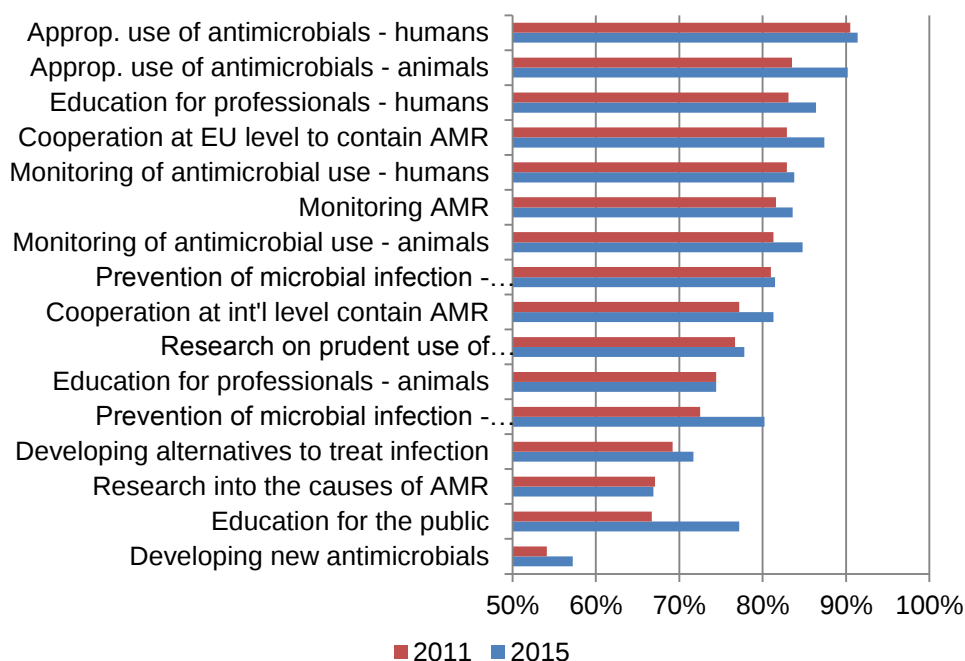
Evaluation question 1: *To what extent do the objectives of the Action Plan address the problems identified in 2011? How well do these objectives correspond to the current needs of tackling AMR within the EU?*

This evaluation question addresses the relevance of the Action Plan's objectives for the needs identified in 2011 and 2015 (i.e. 'current needs' at the time of the evaluation). Judgement criteria and evaluation indicators cover the relevance of the objectives with the problems identified in 2011 and 2015.

3.1.1. The Action Plan's objectives addressed the main issues identified in 2011

More than 90 % of Member State and stakeholder survey respondents agreed that every objective of the Action Plan, for both the human and animal contexts, was relevant to the needs for tackling AMR in 2011.⁹ In half of the areas, more than 80 % of respondents judged them to be 'very relevant' (Figure 3).

Figure 3: Percentage of Member State representative and stakeholder survey respondents finding each objective 'very relevant' for the needs (2011 versus 2015)



Note: Objectives were ordered by percentage of respondents marking them 'very relevant' for the needs in 2011. 'Approp.' and 'int'l' are abbreviations for 'Appropriate' and 'international'.

⁹ Either 'very relevant' or 'somewhat relevant'.

A comparison of AMR policy documents and reports published in 2008-2011, shortly before and in the same year as the Action Plan, indicates that there were several issues that national governments and international organisations consistently identified as being relevant for tackling AMR. A starting point for this comparison is the set of six AMR priority policy areas identified by the WHO in 2011 (WHO 2011a):

1. Commit to a comprehensive, financed national plan with accountability and civil society engagement;
2. Strengthen surveillance and laboratory capacity;
3. Ensure uninterrupted access to essential medicines of assured quality;
4. Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care;
5. Enhance infection prevention and control; and
6. Foster innovations and research and development for new tools.

Four of the WHO priority areas (2, 4, 5 and 6) were explicitly identified as areas where there was a need for action by five action plans, strategies and government reports focused on the EU region that were published near the same time:

- German Antimicrobial Resistance Strategy (Deutsche Antibiotika-Resistenzstrategie — DART) (Federal Ministry of Health, Federal Ministry of Food and Agriculture & Federal Ministry of Education and Research 2008);
- French National Antibiotics Plan, 2011-2016 (Ministère du travail, de l'emploi et de la santé 2011);
- UK annual report of the Chief Medical Officer (2011);
- WHO European strategic Action Plan on antibiotic resistance (WHO/Europe 2011a); and
- Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) recommendations (2011) for future collaboration between the United States and the EU.

The first area, on committing to a comprehensive and financed national plan, was addressed in the WHO/Europe strategic Action Plan (WHO/Europe 2011a), and the UK report called for the UK government to implement a cross-government AMR strategy for 2013-2018 (Chief Medical Officer 2011). The third area, on ensuring access to quality medicines, was highlighted in the WHO European region's plan in the context of its objective on promoting rational use of antibiotics and strengthening surveillance of consumption. There was some variability in the extent to which the plans, strategies and other documents reviewed emphasised animal health relative to human health, but all acknowledged the need to address AMR both in the human and in the animal context.

The EC Action Plan objectives also explicitly addressed the four areas covered by all of the plans, strategies and government reports reviewed, but did not explicitly cover priority 1 (e.g. by including actions for Member States to develop national plans or strategies) or priority 3 (on ensuring access to quality medicines) (Table 6). Nevertheless, the *Guidelines for the Prudent Use of Antimicrobials in Veterinary Medicine* do call for Member States to put in place holistic strategies or plans, thereby addressing priority 1 indirectly. Similarly, although access to medicines was not addressed in the actions or objectives, there was work done in this area under action 8 to support the implementation of national pharmaceutical policies in 15 African countries (EC 2015c).

Table 6: Comparison of WHO priority areas and EC Action Plan objectives

AMR priority policy area identified by WHO in 2011	Corresponding EC Action Plan objectives
1. Commit to a comprehensive, financed national plan with accountability and civil society engagement	[Not included]
2. Strengthen surveillance and laboratory capacity	• Improve monitoring and surveillance in human and animal medicine (actions 9 and 10)
3. Ensure uninterrupted access to essential medicines of assured quality	[Not included]
4. Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care	• Make sure antimicrobials are used appropriately both in humans and animals (actions 1, 2 and 3)
5. Enhance infection prevention and control	• Prevent microbial infections and their spread (actions 4 and 5)
6. Foster innovations and research and development for new tools	• Develop new, effective antimicrobials or alternatives for treatment (actions 6 and 7) • Reinforce research and innovation (action 11)
The WHO highlighted the need for collaborative approaches to AMR (WHO 2011a). AMR was the WHO's 2011 World Health Day theme (and the WHO began organising World Antibiotic Awareness Week in 2015).	Additional EC Action Plan objectives: • Cooperate with international partners to contain the risk of AMR (action 8) • Improve communication, education and training (action 12)

Furthermore, some consultees highlighted areas that they felt the Action Plan had not adequately addressed. The environment is an area that was consistently identified as having not been sufficiently covered in the Action Plan. The environment was addressed in a sub-action under action 8, but only to a limited extent; this sub-action covered the reduction of environmental pollution by antimicrobial medicines, particularly from production facilities. The need to consider the impact of waste from antibiotic manufacturing processes was considered relevant (INT27), but by comparison, the German strategy outlined a wider scope for addressing the environmental aspects of AMR, referring to the release into the environment of antibiotics and resistant infective agents via sewage (from hospitals in particular) and from animal husbandry (Federal Ministry of Health, Federal Ministry of Food and Agriculture & Federal Ministry of Education and Research 2008).

Additional issues were identified through the consultation activities that were not sufficiently covered in the Action Plan. Social science aspects represented one area that was inadequately addressed in the Action Plan (especially under action 12) and that should have been emphasised more in order to affect people's behaviour and use of antimicrobials in the human and veterinary sectors. This issue was raised both in stakeholder workshops and by an interviewee from a European Agency (INT23).

The Action Plan should have placed clearer emphasis on the importance of conserving antibiotics and antibiotic stewardship (Workshops 1 and 2; INT12). Furthermore, the Action Plan did not sufficiently emphasise the need to develop and use vaccines and other tools to prevent and treat infections (Workshops 1 and 2; INT8, INT17, INT20). Two of the three actions related to research and development (R&D) focused mainly on the development of new antibiotics and antimicrobials (actions 6 and 7), while support for vaccines, diagnostic tools and other preventive measures was covered as

only one part of the third action (action 11), alongside several other aspects of research support.

3.1.2. The Action Plan objectives remained relevant in 2015, but a broader set of needs were identified

Similar to the survey results on the relevance of the Action Plan objectives to the needs identified in 2011, survey responses to questions about the relevance of the Action Plan objectives to current needs indicate all of the objectives were considered to be relevant by at least 92 % of respondents.¹⁰ The areas that were considered highly relevant were broadly similar to those of the 2011 situation. The topics of appropriate use of antimicrobials in humans and in animals were considered 'very relevant' by the largest proportion of respondents (91 % for the human health context and 90 % for the animal health context; see Figure 3). The three areas considered 'very relevant' by the smallest proportions of respondents were the development of alternatives for treatment of infection (72 %), research into the causes of AMR (67 %) and development of new antimicrobials (57 %).

National and international action plans and strategies, as well as policy documents, reports and academic articles published in 2015, provided an indication of the current needs for tackling AMR (Table 7). Overall, recognition of AMR as a serious global health threat has grown since the publication of the Action Plan in 2011 (Das & Horton 2016). The action plans and strategies reviewed include those of:

- WHO (WHO 2015a);¹¹
- Germany (Federal Ministry of Health, Federal Ministry of Food and Agriculture & Federal Ministry of Education and Research 2015);
- the Netherlands (Schipper et al. 2015);
- Norway (Norwegian Ministries 2015);
- United States (White House 2015); and
- Switzerland (Swiss Confederation 2015).

Table 7 shows that most of the priorities identified were addressed by multiple policies, indicating that there was broad consensus on the issues to be addressed, at least at a high level.

Table 7: High-level summary of priority AMR policy areas addressed by selected national and international policy documents published in 2015

Policy priority	Countries organisations with policy document that references the priority ^{12,13}	EC Action Plan objective
Promote antibiotic stewardship programmes in human and animal health settings	Netherlands; Norway; Switzerland; United States	Ensure antimicrobials are used appropriately (actions 1, 2 and 3)
Optimise use of antibiotics	WHO	

¹⁰ Either 'very relevant', 'relevant' or 'somewhat relevant'.

¹¹ Developed in collaboration with the OIE and the FAO.

¹² Priorities were not clearly identified in the Netherlands' 2015 Action Plan, so some degree of interpretation was necessary to identify key areas.

¹³ For document references, see list preceding the table.

Evaluation of the EC Action Plan against the rising threats from antimicrobial resistance

Policy priority	Countries organisations with policy document that references the priority ^{12,13}	EC Action Plan objective
(improving access where needed)		
Speed up R&D of new antibiotics, vaccines and/or other therapeutics	Netherlands; Norway; Switzerland; United States; WHO	Develop new, effective antimicrobials or alternatives for treatment (actions 6 and 7)
Support innovation by strengthening public-private cooperation	Netherlands	
Prevent infection, including through use of vaccines and other measures to reduce the need for antibiotics	Norway; Switzerland; United States; WHO	Prevent microbial infections and their spread (actions 4 and 5)
Slow the emergence and/or spread of AMR	Netherlands; Norway; Switzerland; United States	
Improve international collaboration in AMR prevention, surveillance, control, 'one health' and/or R&D	Germany; Netherlands; Norway; Switzerland; United States	Cooperate with international partners (action 8)
Improve monitoring and surveillance (resistance and consumption)	Germany; Netherlands; Switzerland; United States; WHO	Improve monitoring and surveillance (actions 9 and 10)
Advance the development and use of diagnostics to identify and characterise resistant bacteria	Germany; Switzerland; United States; WHO	Reinforce research and innovation (action 11)
Support basic research to better understand AMR	Netherlands; Norway; Switzerland; United States	
Improve understanding of antibiotics and their use among the public, public health professionals and/or veterinarians	Germany; Netherlands; Norway; Switzerland; WHO	Improve communication, education and training (action 10)
Develop political, legal and financial requirements to secure availability and appropriate use of antibiotics	Switzerland	Ensure antibiotics are used appropriately (actions 1, 2 and 3)
Draft an Action Plan and gather data to improve insight on the national situation of AMR in the environment	Netherlands	[Not explicitly addressed in an objective, but partly addressed under action 8]
Develop the economic case for sustainable investment that accounts for needs of all countries	WHO	[Not explicitly addressed in an objective, but the EC funds an OECD study on the cost-effectiveness of AMR policies in human health (EC pers. comm. May 2016)]

The objectives defined in the Action Plan all correspond to priorities identified in other 2015 action plans and strategies, which indicates that they remained relevant in 2015 (Table 7). Some details were also notable. For instance, the German plan emphasises a data-driven approach that supports research and enables rapid responses to emerging resistance threats, and the Norwegian plan highlights fish health (via aquaculture). Some of the plans identified specific targets to achieve, such as either a decrease or no increase in the number of deaths due to antibiotic resistance and a 50 % reduction in avoidable healthcare-associated infections in the Netherlands (Schippers et al. 2015).

In addition, the environment was a specific priority area in one national plan (the Netherlands), and it was emphasised as an issue to address across priorities in the German, Swiss and Norwegian plans. The plans of the WHO, the United States and the Netherlands also specifically focused on improving understanding of how AMR circulates in the environment.

Transmission of resistance from animals and the environment to humans became an increasing concern from 2011 to 2015. Policy documents and academic literature emphasize that the environment must not be overlooked in addressing AMR and that more knowledge is needed about AMR transmission in the environment and how to address it (CDDEP 2015; OIE 2015a; WHO 2015a; Dar et al. 2015; O'Neill Review 2015d; Swiss Confederation 2015; Schippers et al. 2015; Federal Ministry of Health, Federal Ministry of Food and Agriculture & Federal Ministry of Education and Research 2008, 2015; Norwegian Ministries 2015). Resistance and antibiotics could circulate through poor sanitation, hospital waste and agriculture (INT18). There is a need to improve our understanding of the role of the microbiota in the environment and how it contributes to AMR transmission (INT15). More surveillance of waste from healthcare settings could be used to gather data about the presence of antimicrobial residues and their potential impacts; antimicrobial resistance and residues in soil could also be studied (INT19).

The international dimension of AMR grew in importance from 2011 to 2015. Interviewees commented that AMR is increasingly a trans-boundary issue and that transmission of antibiotic-resistant bacteria is likely to occur through migration, business travel and/or tourism (INT8, INT12, INT17, INT21). They suggested that the EU would benefit from having a more outward-looking Action Plan, taking into account what happens beyond the boundaries of the EU (INT17, INT24). Årdal et al. (2016) highlighted five areas where international collaboration generally needs to be strengthened globally: surveillance of AMR and antimicrobial usage, infection control and prevention, universal access to antimicrobials, responsible use, and innovation. As was the case for the assessment of needs in 2011, more recent action plans and strategies highlight the importance of access to medicines and the unaffordability of 'last-resort' medicines in developing countries (e.g. WHO 2015a; Laxminarayan et al. 2016), as well as sustained financing to those countries to address these challenges (e.g. WHO 2015a; Mendelson & Gopinathan 2015).

Global monitoring and surveillance was widely identified as an issue of growing importance. Documents identify a need for coordinated and harmonised surveillance to monitor AMR; the worldwide use and circulation of antimicrobial agents (Årdal et al. 2016; WHO 2015a; O'Neill Review 2015c; Schippers et al. 2015); and drug quality (O'Neill Review 2015e). Two interviewees suggested that EU policy should increase monitoring of international food supply chains and movements of people (INT8, INT17). The animal health and environmental sectors particularly are seen to lack global surveillance programmes and are considered to be chronically underfunded (Dar et al. 2015). In addition, a WHO representative indicated that one specific area where EU support could contribute further was in surveillance: non-EU countries in the European region need to build their capacity to do monitoring and surveillance in order to better understand the issues they face, and European agencies, such as the ECDC,

could contribute valuable technical support if they actively engaged with countries outside the EU (in addition to the guidance and protocols currently provided) (INT24).

The need for vaccines, rapid diagnostics, antimicrobials and other tools and research that would help treat and prevent infection and thus reduce the need for antimicrobials remained acute in 2015, as indicated by the coverage of these issues by all action plans reviewed (Table 7). Consequently, the need to invest in research and development to tackle AMR remained highly relevant in 2015. The O'Neill review called for increased funding for early-stage research (O'Neill Review 2015c), a global innovation fund for diagnostics (O'Neill Review 2015a), interventions to incentivise drug innovation (O'Neill Review 2015b), and investment into vaccines and other tools (O'Neill Review 2016). As discussed in EQ6, AMR was an underfunded research area globally, although the EU made substantial contributions in this area. As discussed in the previous section, the evidence indicates that there may be a need for EU support to place greater emphasis on a wider range of research and development areas, that is, beyond the development of new antimicrobials.

The holistic, 'one health' approach adopted by the Action Plan was very relevant for tackling AMR in 2015 (Workshop 1; INT2, INT3; WHO 2015a; Gibbs 2014; White House 2015). Some areas were identified, however, in which the 'one health' approach in the Action Plan was limited, namely, coverage of environmental issues (INT18); addressing social factors, such as reasons for prescribing behaviours (INT17); and public health challenges faced by vulnerable populations (case study 2, Appendix N). Open-text responses to a survey question about how the Action Plan could have been made more holistic included considering the role of alternative therapies (phytotherapeutic and homeopathic remedies; complementary and alternative medicine) and considering the impact of pathogen exposure on workers (veterinarians as well as and workers in slaughterhouses, in food factories and on farms).

3.2 Extent to which areas for EU action were distributed in line with EU and Member State competences

Evaluation question 2: *Are the areas for EU action appropriate in view of the distribution of EU and national competences?*

This evaluation question addressed the appropriate allocation of actions to the EU and Member States. Judgement criteria and evaluation indicators covered the distribution of actions in line with EU and Member State competences.

3.2.1. All of the actions were aligned with EU and Member State competences

There are three types of EU competence: areas where the EU could take exclusive action, areas where the EU and Member States share competence, and areas where the Member States take exclusive responsibility for legislation (2010/C 83/01).¹⁴ The EU's competences in the sectors relevant for AMR vary in this regard. In particular, the EU has less competence on human health than on animal health, and, as a result, EU action in human health must focus on 'soft' approaches, such as issuing

¹⁴ According to Consolidated Versions of the Treaty on European Union and the Treaty on the Functioning of the European Union (2010/C 83/01), the European Union has exclusive competence in terms of the customs union, competition rules for the internal market, Eurozone monetary policy, and conservation under the common fisheries policy and the common commercial policy. Both the EU and Member States share competences in the internal market; agriculture and fisheries; the environment; social policy; economic, social and territorial cohesion; transport; consumer protection; energy; freedom; security and justice; common safety in public health; and trans-European networks. Finally, Member States have exclusive competence over human health, industry, tourism, culture, education and training, administrative cooperation and civil protection, while the role of the European Union is to support Member States in pursuing their goals in these areas.

recommendations and guidance for Member States in such areas such as the prudent use of antimicrobials.

Overall, the Action Plan consists of appropriate actions for the European Commission and Agencies, and the nature of each action varies appropriately given EU and Member State competences. Among survey respondents who answered a question asking whether the Action Plan identified actions best dealt with at EU level, 84 % (114 out of 135) either agreed (78 out of 135) or strongly agreed (36 out of 135) that actions best dealt with at EU level were identified.

Due to differences in the EU's competences in different sectors (with notable differences in public health versus agriculture and animal health), the character of actions varied by sector. For animal health, where the EU has more competence, three associated actions (actions 2, 3 and 5) focused on EU legislative action. Member States have responsibility on human health issues, in line with subsidiarity rules related to public health policy, and Action Plan actions in this area focused on promoting and monitoring Member State activities (actions 1 and 4). For instance, where the human health-related actions focused on implementation and monitoring of progress on existing council recommendations (actions 1 and 4), the animal health-related actions included the introduction of recommendations for prudent use in veterinary medicine (action 3) as well as a strengthened regulatory framework for veterinary medicines and medicated feed (action 2) and a new animal health law (action 5). Similarly, while the Action Plan included actions to strengthen surveillance on AMR and antimicrobial consumption in humans (action 9) and animals (action 10), the action in the animal health context entailed introducing a legal requirement for monitoring and reporting of AMR by Member States, while in the human health context the action focused on the role of the ECDC in monitoring and surveillance.

Member States share responsibility with the EU for supporting research and innovation. Action 11 centred on EU action to support research and assist Member States and other countries with coordinating their AMR research programmes. Action 8 focused on the EU's role in multilateral and bilateral cooperation. Action 12 focused on EU action to monitor EU-level public awareness about AMR.

Actions 6 and 7 addressed EU actions related to an EU programme for supporting antimicrobial development (involving industry engagement), including treatment alternatives. This is an area where survey respondents reported potential issues with the appropriate allocation of responsibilities. Concerns were also expressed regarding the appropriate use of antimicrobials in animals (action 3). Consultees expressed concern about the degree of disparity across Member States in various aspects of AMR, including the extent to which Member States could invest the resources needed to support research and development, and improve their monitoring and surveillance systems (survey comments); address human health aspects of AMR (INT12, INT14, INT23); and the extent to which action was being taken by Member States (survey comments).

Respondents were divided about the appropriate allocation of responsibilities, however. Some suggested that the EU should take greater responsibility to reduce these disparities and ensure implementation of harmonised measures to address AMR across countries; others indicated that Member States must take greater responsibility for tackling AMR.¹⁵ One Commission official (INT12) felt that the Action Plan should have included a mechanism to provide more support for Member States, which could

¹⁵ One aspect highlighted was differences in the degree to which different Member States monitor usage of antimicrobials in animals, an issue that has been addressed under the Action Plan through the introduction of a legal basis for this monitoring. This legal basis is included in the proposal for a new regulation on veterinary medicinal products.

have taken the form of a programme to help Member States design and coordinate their policies, or measures to encourage regional cooperation. A similar point was raised by another interviewee (INT24), who noted that the WHO global Action Plan had called on countries to implement national action plans. As noted in EQ1, the Commission has called on Member States to put in place holistic strategies and/or action plans for addressing AMR under the *Guidelines for the Prudent Use of Antimicrobials in Veterinary Medicine*.

4. EFFECTIVENESS — FINDINGS AND CONCLUSIONS

This section reports the findings and conclusions on evaluation questions related to the effectiveness of the EC Action Plan.

4.1 Extent to which actions were effective at improving treatment of infections in humans and animals

Evaluation question 3: *To what extent have the actions been effective at improving treatment of infections in humans and animals?*

This evaluation question addressed the contribution of the Action Plan to improving treatment of infections in human and animals. Judgement criteria and indicators covered the following areas related to human health: (i) total antimicrobial consumption for use in humans, (ii) appropriate use of antimicrobials in humans and (iii) approaches to treating infections in humans. In animal health, the areas covered included: (i) antimicrobial consumption for use in animals; (ii) prudent use of antimicrobials in veterinary medicine; and (iii) rules, guidance and authorisation requirements for veterinary medicines and medicated feed. The evaluation covered R&D through (i) support for collaborative R&D to bring new antimicrobials to patients, (ii) conditions for the introduction of new veterinary antimicrobials and (iii) reinforcement and coordination of research efforts.

Changes in antimicrobial resistance and consumption patterns are reported in this section, but these could not be linked to the Action Plan because it was too early at the time of the evaluation to attribute changes observed to the Action Plan and because any observed effects could not be disentangled from other AMR policy initiatives that were taking place prior to and in parallel with the Action Plan. Variability was observed across Member States in terms of patterns of drug usage in humans and animals. It was also too early to assess the impact and outcomes of research and innovation projects.

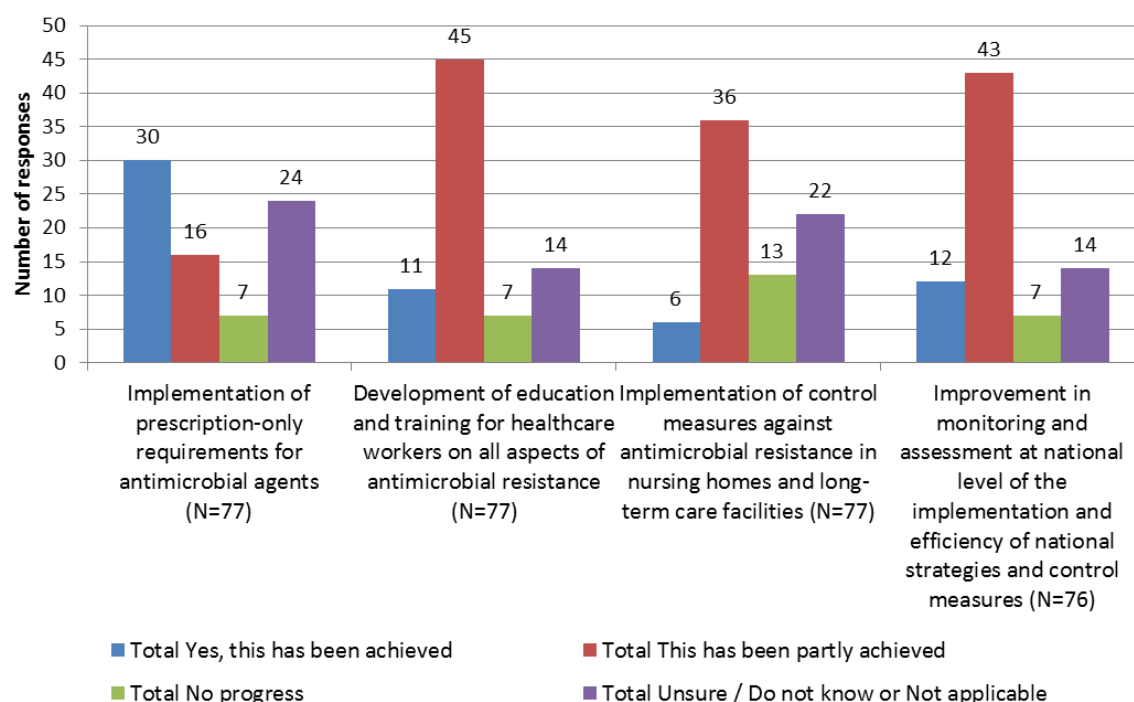
4.1.1. Policies to address the use of antimicrobials in human medicine improved in some areas

This section covers changes in the use of antimicrobials in human medicine and related policy developments on this issue.

4.1.1.1. The greatest policy achievement was the implementation of prescription-only requirements for antimicrobial agents

Policies to address the use of antimicrobials improved overall during the period of the Action Plan evaluated for this study. In particular, action 1 focused on the implementation of the Council Recommendation of 15 November 2001 on the prudent use of antimicrobials in human medicine. Survey respondents indicated that on each of four aspects, objectives had been achieved at least to some extent (Figure 4).

Figure 4: Survey results on the reported effectiveness of the implementation of aspects of the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC)



Source: Stakeholder and Member State surveys (2016).

The greatest achievement was observed in the implementation of prescription-only requirements for antimicrobial agents; 39 % of survey respondents (30 out of 77) indicated that implementation had been achieved, and 21 % (16 out of 77) indicated that it had been partly achieved. This is in line with the findings of a study on the implementation of the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (Dumartin 2015), which found that all but one country (Italy) transposed the prescription-only requirement in their national laws. In addition, Dumartin (2015) found that 23 countries reported that this legislation was being enforced, mainly through inspections in pharmacies.

Participants at both stakeholder workshops commented that despite this legislation, however, patients continued to obtain antibiotics without a prescription (from pharmacists or online sellers). This was supported by the Special Eurobarometer survey on AMR (TNS Opinion & Social 2013), which found that large proportions of respondents from some countries (e.g. 18 % from Romania, 15 % from Greece and 10 % from Cyprus) used antibiotics without a prescription. Another study identified socioeconomic and health system factors that drive pharmacists to provide antibiotics without prescription in Romania (Ghiga & Stålsby Lundborg 2016).

The development of education and training for healthcare workers on AMR was identified by most survey respondents as having been achieved (11 out of 77, or 14 %) or partly achieved (45 out of 77, or 58 %). This observation corresponds with the findings of the report on the implementation of Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine, which notes that AMR and prudent use of antimicrobials was part of education curricula for pharmacists and medical doctors in the majority of Member States (Dumartin 2015). The second report assessing the implementation of Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections, also observed that core competencies for infection control and hospital

hygiene have been established (ECDC 2013c) and are being used by Member States (EC 2014a). However, one interviewee (INT14) from an international organisation, who indicated that education and training of healthcare workers had been partly achieved, noted that, although core competencies related to AMR for healthcare workers have been published at EU level, without conducting research with healthcare workers on the ground, it is difficult to know the extent to which those core competencies are being delivered through training in Member States.¹⁶ This helps to explain why a majority of survey respondents indicated that this aspect had been partly achieved, rather than fully achieved.

Implementation of control measures against AMR in nursing homes and long-term care facilities were identified by more than half of survey respondents as having been achieved (6 out of 77, or 8 %) or partly achieved (36 out of 77, or 47 %). However, this was also the area where the highest proportion of respondents indicated that no progress had been made (13 out of 77, or 17 %). The report on the implementation of the recommendation on the prudent use of antimicrobial agents in human medicine found that more countries had developed infection control guidelines for nursing homes and LTCFs (24 in 2015 versus 20 in 2011) (Dumartin 2015). However, the report noted that guidelines on prudent use of antimicrobials in these settings are still rare and that the number of countries with national requirements or recommendations for the number of infection control doctors and nurses in nursing homes has actually decreased to only three (from four in 2011) (Dumartin 2015). The report assessing the implementation of the recommendation on patient safety identified ensuring compliance with infection control guidelines (in all settings) as an area where further progress is needed (EC 2014a).

Antimicrobial stewardship was identified by participants in both stakeholder workshops as a way to promote the prudent use, and support the conservation, of the effectiveness of existing antibiotics. An interviewee (INT18) from an international organisation emphasised that antimicrobial stewardship¹⁷ should be provided in each facility by an expert in infection and AMR in order to guide physicians' decision-making on the treatment of infection.

The 2015 report on the implementation of the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine found that hospitals in 20 countries were required to implement antimicrobial stewardship activities (Dumartin 2015). Participants in the second stakeholder workshop commented that knowledge about infection prevention and control is often significantly better within hospitals than outside them, so it is important to look at improving practice in other settings. A report published the year before on the implementation of the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections (EC 2014a), identified progress in this area in the context of LTCFs: it said that national performance indicators for antimicrobial stewardship (and for infection prevention and control) had been developed and would be used to monitor Member States' work in these areas.

¹⁶ Some participants at the second stakeholder workshop also commented that there was insufficient emphasis on the importance of medical professionals' education in the Action Plan.

¹⁷ Antimicrobial stewardship aims to educate and persuade prescribers of antimicrobials to follow evidence-based prescribing, in order to stem antibiotic overuse and thus antimicrobial resistance. It is a multifaceted intervention which aims to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use and to reduce healthcare costs without adversely impacting quality of care (Dellit et al. 2007).

The concept of stewardship is well established at EU level and the country level in some countries. Examples of stewardship programmes were identified in the UK, the Netherlands and Portugal. One UK stewardship programme, the TARGET online toolkit, was the focus of case study 3 (Box 1 and Appendix N). The case study found that the toolkit's uptake was lower than that of another UK antimicrobial stewardship toolkits targeting hospitals, but it was successful in presenting consistent messages across healthcare providers, patients and services.

Case study 1 focused on trends in HAI indicators in the Netherlands and Portugal (Appendix N) and also identified evidence of progress on establishing antimicrobial stewardship efforts in these two countries. In 2013, the Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibioticabeleid — SWAB) introduced multidisciplinary antibiotic teams (known as A-teams) in every hospital with the aim to provide training and advice and to authorise use of antimicrobials for special indications (Hospital Pharmacy Europe 2013). In Portugal, antibiotic stewardship programmes, which included education for healthcare professionals, were being implemented in all health facilities from the end of 2015 (Neves et al. 2015).

Improvements in monitoring and assessment at national level of the implementation and efficiency of national strategies and control measures was also identified by most respondents as having been achieved (12 out of 76, or 16 %) or partly achieved (43 out of 76, or 57 %). The report on the implementation of the Council Recommendation on the prudent use of antimicrobial agents in human medicine noted some progress in the area while stressing the need for further action in linking AMR action plans to strategies for patient safety and HAI prevention and control and on the use of quantitative targets. While a larger number of countries had indicators in place to monitor the implementation of their national Action Plan (18 in 2015 versus 12 in 2008), eight countries were found not to have any strategy or Action Plan, and where there were strategies in place, these were not always linked to strategies for patient safety and HAI prevention. Among countries that had set progress indicators, fewer than half also included quantitative targets (Dumartin 2015).

Overall, EU-level progress was identified in the second report assessing the implementation of the Council Recommendation of June 2009 on patient safety, including the prevention and control of healthcare associated infections, in terms of (i) adoption of general and specific case definitions for HAIs, (ii) provision of a standardised methodology and framework for the national surveillance of HAIs and (iii) improvements in the collection of data on HAIs through the ECDC point prevalence survey (EC 2014a). The report also highlighted a need for more efforts on targeted surveillance of HAIs in surgical site infection, in intensive care units and in nursing homes and other LTCFs (EC 2014a). In line with the finding from the report, one interviewee (INT14) from an international organisation highlighted obstacles to the PPS conducted by the ECDC in LTCFs, including many countries' reluctance to participate and the difficulty of establishing a representative sample of healthcare facilities in each country. The same interviewee (INT14) also identified a need for monitoring of multi-resistance in gram-negative bacteria, particularly in those which have been identified as bacteria causing HAIs. A second interviewee (INT18) from an international organisation supported increased monitoring of multi-resistant bacteria and drew attention to the danger of suboptimal practices for controlling the spread of infections in some healthcare facilities. The interviewee placed particular emphasis on the need to increase capacity to isolate patients with multi-resistant bacteria within healthcare facilities.

4.1.1.2. Evidence suggests there was no change in antimicrobial consumption by humans annually in the EU since 2011

Although policies improved from 2011 to 2015, the data show that for most classes of antimicrobials in most Member States, there was no statistically significant change in

average annual consumption of antimicrobials for use in humans in the years following the introduction of the Action Plan.

Figure 5 illustrates the differences among countries in consumption of antibacterials outside of hospitals (Antibacterial Consumption Calculator (ATC) group J01) for 30 EU/EEA countries in 2014.¹⁸ In that year, consumption varied by a factor of 3.2 between the highest consumption country (34.0 defined daily doses (DDD) per 1 000 inhabitants per day, in Greece) and the lowest (10.6, in the Netherlands).¹⁹ Figure 6 indicates that there may be a north-south gradient, with the lowest consumption in the north of Europe (e.g. the Netherlands and the Scandinavian countries) and the highest consumption in the south of Europe (e.g. Greece and Romania).

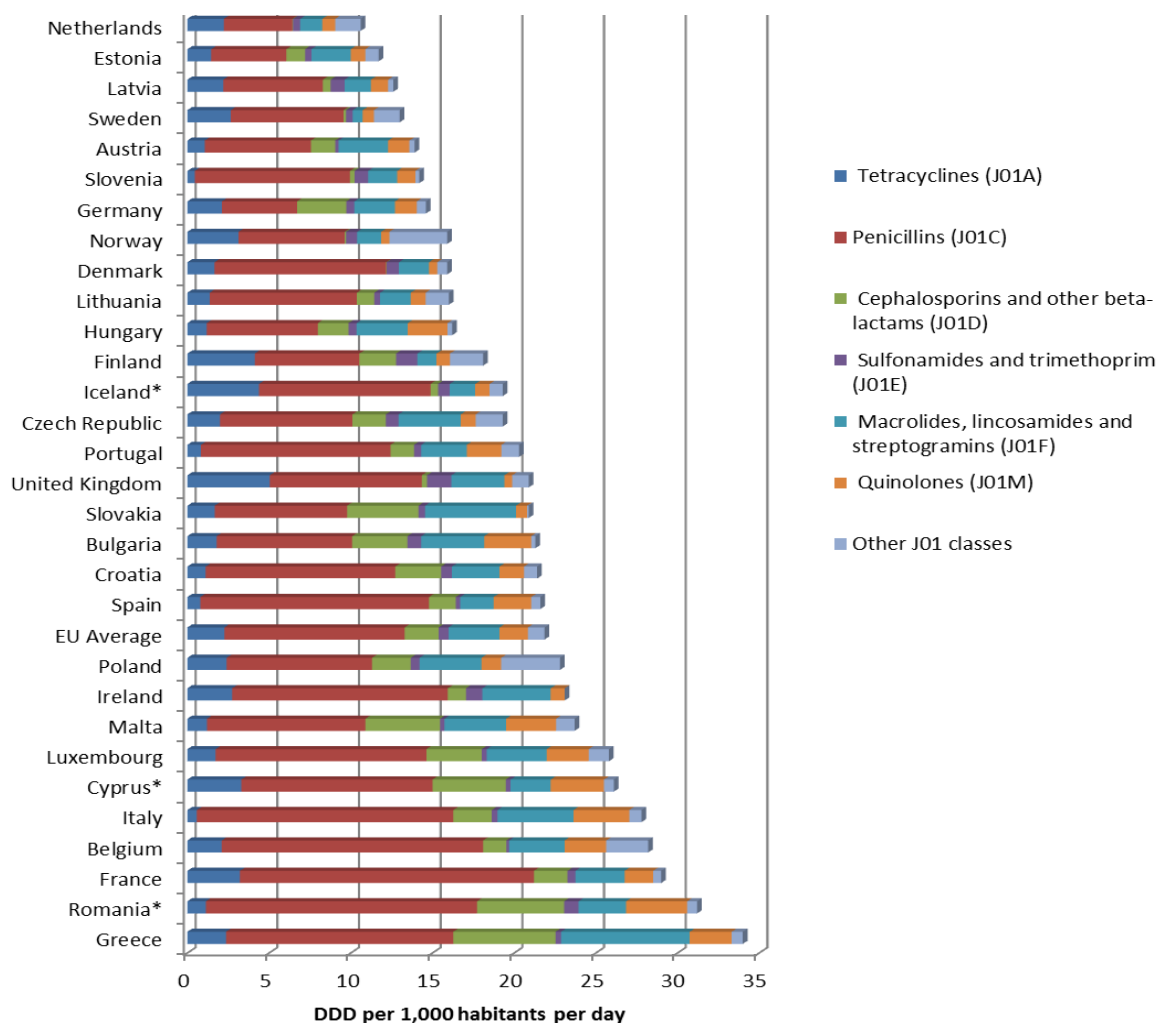
In addition to the data from 2014, consumption data for 30 EU/EEA countries were available covering the period 2011-2014 for all antibacterials used outside of hospitals (J01) as well as for a subgroup of antibacterials known as J01C (which includes penicillins, beta-lactamase inhibitors (J01CR) and penicillins with extended spectrum (J01CA)). J01C was selected because, as shown in Figure 5, in terms of consumption, it is the largest subgroup of antibacterials. The change in the population-weighted EU/EEA mean consumption of J01 antibacterials between 2011 and 2014 was very small: from 21.6 DDD per 1 000 inhabitants per day in 2011, to 21.7 in 2012, 22.3 in 2013 and then 21.9 in 2014 (Appendix M).

The average annual change in consumption was only statistically significant in Cyprus, Iceland and Portugal (consumption fell) and Croatia, France and Greece (consumption increased). Reductions in the consumption of some classes of antibacterials in some countries may have been offset by increases in consumption elsewhere. In 2011, consumption varied by a factor of 3.1 between the highest consumption country (35.7, in Greece) and the lowest (10.4, in the Netherlands), a comparable magnitude to the difference observed in 2014.

¹⁸ The most recent year for which data are available.

¹⁹ The population-weighted EU/EEA mean consumption was 21.9 DDD per 1 000 inhabitants per day.

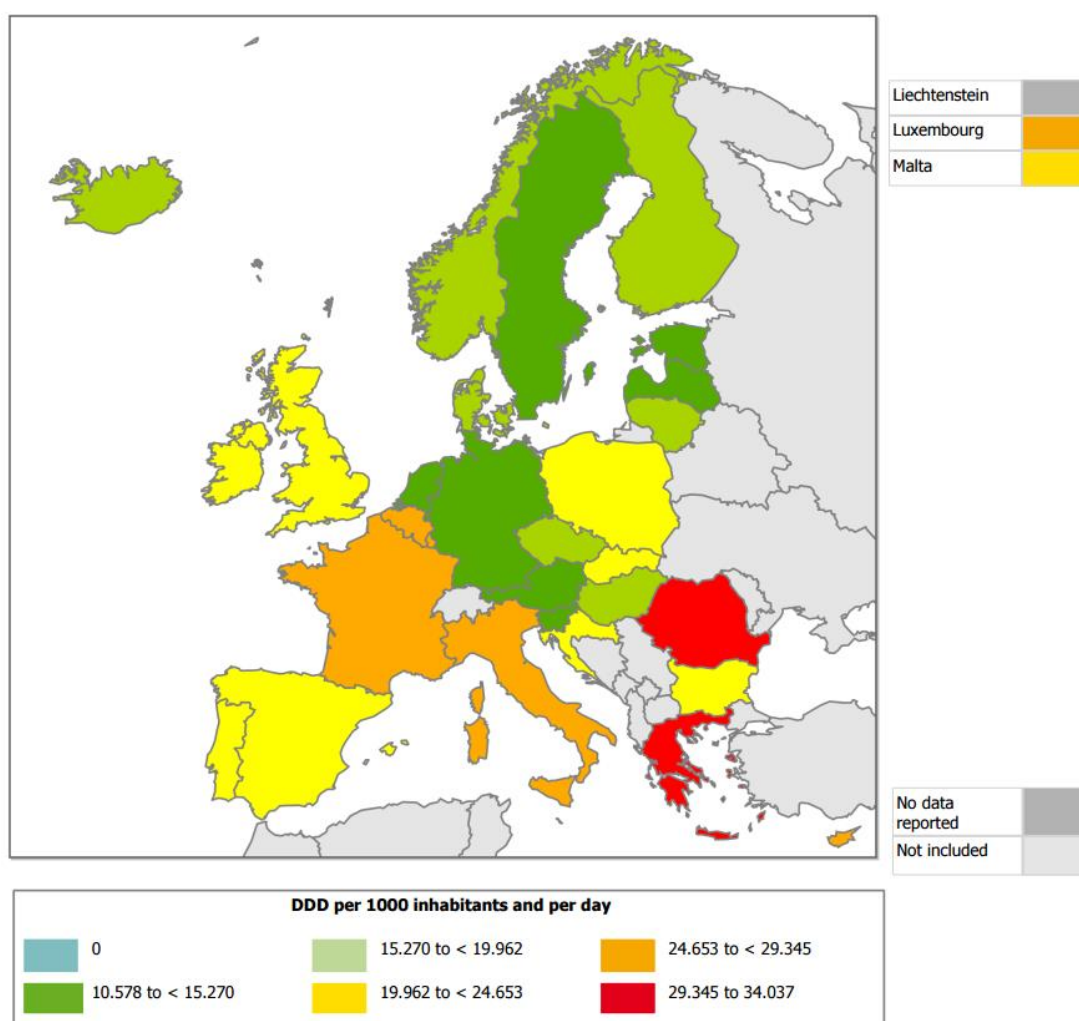
Figure 5: Distribution of antibacterials consumption (ATC group J01) in EU/EEA countries, and average across EU (2014)



Source: RAND Europe, using ECDC data.

Note: Pertains to consumption outside of hospitals, with the following exception: Total care data are reported for Cyprus, Iceland and Romania (i.e. including the hospital sector) (indicated with *).

Figure 6: Antibacterial consumption (ATC group J01) outside of hospitals in EU/EEA countries (2014)



Source: ESAC database http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/geo-distribution-consumption.aspx.

Note: Pertains to consumption outside of hospitals, with the following exception: Total care data are reported for Cyprus and Romania (i.e. including the hospital sector).

Consumption of antibacterials in the hospital sector represented a small but important proportion of total consumption due to the link with HAIs (e.g. in 2012, consumption was 2.0 DDD per 1000 inhabitants per day). Similar to the analysis of overall consumption in the EU, the most recent annual report on surveillance of antimicrobial consumption in the hospital sector in Europe identified no significant trends in mean consumption for the period 2007-2012 (ECDC 2014f).

Commenting on the factors underlying trends in antimicrobial consumption in human medicine, two interviewees (INT12, INT18, representing the research industry and an international organisation, respectively), noted weak compliance in some Member States with regulations on non-prescription access to antimicrobials, with one (INT12) citing Cyprus, Greece and Italy as countries with relatively high non-prescription sales over the counter. The countries that have succeeded in reducing consumption, according to the same interviewee, are those that have well-developed national strategies and action plans.

4.1.1.3. Consumption patterns shifted towards greater dependence on broad-spectrum relative to narrow-spectrum antibacterials in humans

Broad-spectrum antibacterials are less targeted and kill a wider range of bacteria (i.e. not only the bacteria causing a particular disease). Therefore a shift towards more use of narrow-spectrum antibacterials (i.e. a reduction in the ratio between broad- and narrow-spectrum antibacterials) would be viewed as an improvement in prescribing practices. The ratio is a quality indicator for assessing the appropriateness of outpatient antibiotic use that was developed and agreed through a consultation with 27 experts from across Europe (Coenen et al. 2007).

Analysis of European Surveillance of Antimicrobial Consumption (ESAC) data was used to identify ratios of the consumption of broad-spectrum antibacterials (encompassing penicillins, cephalosporins and macrolides) to consumption of narrow-spectrum antibacterials for 30 EU/EEA countries in the years 2011-2014 (Appendix M).²⁰ There was a high degree of variation between countries in terms of the ratio of broad-spectrum to narrow-spectrum antibacterials in all years. For example, in 2011, variation ranged from 0.17 in the highest-performing country (Sweden) to 142.7 in the lowest-performing country (Malta). This means that for each unit (e.g. DDD) of narrow-spectrum antibacterials used in Malta, 142.7 units of broad-spectrum antibacterials were used, whereas in Sweden, more than five units of narrow-spectrum antibacterials were used for each unit of broad-spectrum antibacterials.

In 2014, the ratio in the two highest-performing countries (Norway and Sweden) was 0.21 and 0.37, whereas the ratio in the two lowest-performing countries (Greece and Italy) was 606.81 and 184.26. This indicates that the variation in performance among countries worsened during the period 2011-2014. Although this was driven by a worsening in the performance of countries with a high ratio, rather than by any change in the performance of countries with a low ratio, the median ratio also increased across countries, from 7.7 in 2011 to 9.5 in 2012, before stabilising, at 11.3 in 2013 and 11.2 in 2014.

Thus, on two measures of change in the ratio of broad-spectrum to narrow-spectrum antibacterials (i.e. change in the gap between best and worst performers and change in the median performance), consumption patterns shifted towards greater dependence on broad-spectrum antibacterials relative to narrow-spectrum antibacterials during the period of the Action Plan's implementation, which was contrary to the objectives of the Action Plan.

4.1.1.4. There was no change in average antimicrobial consumption in EU long-term care facilities

Evidence on antimicrobial use in long-term care facilities was gathered from the PPS survey titled Healthcare-associated infections in long-term care facilities (HALT). The first HALT survey was conducted from May to September 2010 and involved 722 LTCFs across 28 European countries (ECDC 2014a). Between April and May 2013, 1 181 LTCFs in 19 European countries participated in the second PPS (HALT-2) (ECDC 2014a).

In 2010, the crude prevalence rate of residents receiving at least one antimicrobial agent was 4.3 %, and in 2013, the rate was almost unchanged, at 4.4 % (in 2013 this ranged from 1 % in Hungary to 12.1 % in Greece). Thus the PPS indicated that there was no statistically significant difference in the average consumption of antimicrobials

²⁰ The ratio cannot be used as the sole indicator of the appropriateness of antimicrobial use, however, unless ratios are reported alongside other data (e.g. total consumption data) and alongside such information as the extent to which actions aimed at containing the risks of spreading AMR have been effective (addressed in EQ4). Another caveat is that the ratio does not take account of the fact that many narrow-spectrum antibacterials are being taken off the market, while broad-spectrum antibacterials are increasingly available (Theuretzbacher 2015). As a result, a causal link cannot be established between relative availability of broad- and narrow-spectrum antibacterials and levels of appropriate use.

among patients at LTCFs. However, this comparison should be treated with caution due to limitations in the data, not least because the number of countries included in the survey decreased between 2010 and 2013.

4.1.2. Overall sales of veterinary antimicrobials in the EU decreased since 2011, and proposals on veterinary medicines and medicated feed were expected to bring further improvements in this area

The Action Plan highlighted that there are 'significant differences' between Member States in the sale and administration of antimicrobials for use in animals and it called for the introduction of recommendations for prudent use in veterinary medicine.

4.1.2.1. Rules, guidance and authorisation requirements for veterinary medicine improved

The European Commission produced a set of guidelines in 2015 for the prudent use of antimicrobials in veterinary medicine (EC 2015b) under Action Plan action 3. The guidelines provide recommendations on general principles for prudent use; awareness raising; enforcement and sanctions; disease prevention and reducing the need for antimicrobials; surveillance and monitoring; and national strategies.

Commenting a relatively short time after their adoption, survey respondents and interviewees²¹ were broadly positive about the anticipated impact of the guidelines. For example, the majority of survey respondents who indicated that they were familiar with the recommendations (83 %, 75 out of 90) believed that they would have a positive impact on the prudent use of antimicrobials in veterinary medicine. Interviewees (INT2, INT3) from a European-level body asserted that the guidelines had the potential to help replace traditional modes of antimicrobial use with better practices in veterinary medicine. These two interviewees also noted that some systematic applications of antimicrobials were important for animal production. They gave the example of treating cows with antimicrobials at the end of the lactation period, which, the interviewees argued, had not led to any significant occurrence of AMR. An independent expert (INT7) commented that the guidelines would be of most use to countries at a less advanced stage in developing policies on the use of veterinary antimicrobials because they aggregated the measures taken by countries that already had well-developed national action plans covering these issues and presented them in a way that allowed less advanced countries to adopt them as part of their own national strategy.

There was also evidence of a number of other actions taken at Member State level since the publication of the Action Plan to improve prudent use of antimicrobials in animals. According to a joint report endorsed by the EMA's Committee for Medicinal Products for Veterinary Use (shortened to CVMP) and the Committee for Medicinal Products for Human Use (shortened to CHMP),²² Denmark, France and the Netherlands had already introduced guidelines which classified different antimicrobials as 'first line', 'second line' or 'last resort' in order to promote their prudent use (EMA 2014).²³ These guidelines were based on country-specific factors, including the local resistance

²¹ INT21, INT17, INT7, INT4, INT2, INT3.

²² This report was prepared by the Antimicrobial Advice Ad Hoc Expert Group, which includes representatives from the EMA's Committee for Medicinal Products for Veterinary Use (CVMP) and the CVMP Antimicrobials Working Party, the EMA's Committee for Medicinal Products for Human Use (CHMP) and the CHMP Infectious Disease Working Party, EFSA, and ECDC.

²³ For example: Danish Veterinary and Food Administration (2013); Ministère de l'Agriculture, de l'Agroalimentaire et de la Forêt (2012); MARAN (2013).

situation. According to the EMA, nine EU countries²⁴ built on those classifications by banning the use of certain critically important antimicrobials (CIAs),²⁵ such as third- and fourth-generation cephalosporins, as first line treatments (EMA 2014). Examples of voluntary controls include requirements for susceptibility testing of pathogens before CIAs are used, which have been introduced in countries including Denmark, the Netherlands and Sweden.

The EMA reported on the impacts of some of these measures (EMA 2014). The results of measures adopted since the Action Plan were not provided, but reported impacts achieved by early adopters were identified as examples of the potential effectiveness of the types of controls on use of veterinary antimicrobials recommended by the Action Plan. The results reported by the EMA showed a reduction in the occurrence of resistance to antimicrobials in bacteria such as *Escherichia coli* and *Campylobacter* following the introduction of controls. In one case highlighted (the Netherlands), however, the reduction in occurrence of resistance was accompanied by an increase in the number of *Escherichia coli* infections.

There were limited data available on trends in the prudent use of antimicrobials in veterinary medicine since the publication of the Action Plan with which to establish the effectiveness of the above measures. Studies referenced by EMA reports with respect to trends in figures on prudent use were based on data gathered prior to the Action Plan (EMA 2014), while the EFFORT (Ecology from Farm to Fork Of microbial drug Resistance and Transmission) project, a Seventh Framework Programme for Research and Technological Development (FP7) project that assessed the effects of AMR in the food chain, had not produced any data at the time of the evaluation.

Case study 7 (Appendix N) examined the successful reduction of antimicrobial use in aquaculture in Norway through prioritisation of vaccines as a method of reducing therapeutic use of antimicrobials. Improvements in prudent use, achieved between 1987 and 2007, arose through a combination of factors, including improved rules, guidance and authorisation requirements (e.g. that antimicrobials for use in aquaculture be prescribed by a veterinarian and that fallowing periods be used to break reinfection cycles), in combination with the availability of high-quality vaccines effective against disease (e.g. the bacterial infections coldwater vibriosis and furunculosis).

The Action Plan's action 2 was to 'strengthen the regulatory framework on veterinary medicines and on medicated feed'. It entailed the following four sub-actions: (i) ensuring 'appropriate warnings on labels of veterinary antimicrobials', (ii) considering 'restrictions on regular or off-label use of certain CIAs for humans in the veterinary sector', (iii) considering 'amendments to rules on advertisement of veterinary antimicrobials' and (iv) revisiting authorisation requirements for veterinary antimicrobials.

In September 2014, the European Commission adopted proposals to revise legislation on veterinary medicinal products (VMPs) (EC 2014c) and on medicated feed (EC 2014b,c,d). The two legislative proposals address the four areas identified in action 2, and consultees expected that the proposals would be beneficial for addressing the relevant objectives. Participants in both stakeholder workshops highlighted the

²⁴ Belgium, the Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Sweden and the UK.

²⁵ CIAs for human medicine, as defined by the WHO, are antimicrobial substances which fulfil the following two criteria: (i) antimicrobial agents that are used as sole therapy or one of few alternatives to treat serious human disease and (ii) antimicrobial agents that are used to treat diseases caused by either (a) organisms that may be transmitted via non-human sources or (b) organisms that may acquire resistance genes from non-human sources.

legislative proposals as important achievements in the context of appropriate use of antimicrobials in animals. Position papers published by stakeholder organisations similarly agreed that the Commission's legislative proposals were a positive step towards combating AMR, but there were contrasting views on the anticipated impact of specific aspects. The legislation had not been adopted at the time of the evaluation, precluding any evaluation of its effectiveness.

The sub-action under action 2 on ensuring 'appropriate warnings and guidance on the labels of veterinary antimicrobials' (EC 2011, 7) was addressed in the proposal on VMPs, which states that the packaging of all VMPs sold in the EU should include specific information on the use of antimicrobials and restrictions in the summary of product characteristics (which should be reflected in the package leaflet). The proposal on VMPs also introduces, *inter alia*, the possibility to restrict off-label use of antimicrobials; strengthens prescription requirements; and includes limitations for retailing of antimicrobials by veterinarians.

The VMP proposal provides additional rules regarding advertising, for example, that advertising should not provide misleading information or lead to overconsumption. The VMP proposal also states that marketing authorisation should be refused for any antimicrobial veterinary medicinal product if the antimicrobial is reserved for use in human medicine. It includes a ban on authorisation for any veterinary antimicrobial products intended for growth promotion. Furthermore, the proposal requires a more comprehensive risk assessment for marketing authorisation procedures for antimicrobials and introduces the possibility for post-authorisation studies, to ensure that the benefits outweigh the risks and that the benefit to risk balance remains positive regarding AMR.

The European consumer organisation (BEUC) (2015) argued that this proposal was too vague regarding the 'misuse' of antimicrobials; BEUC called for a ban on prophylactic use of antimicrobials contained in the medicated feed proposal to be included in the veterinary medicines proposal. In contrast, the Federation of Veterinarians of Europe (FVE) (2014) stated that some of the more restrictive elements of the proposal may jeopardise animal welfare, particularly with regard to off-label use of antimicrobials. FVE (2014) argued that there was often no specific product available to treat an animal, and that veterinarians must therefore be allowed to use products outside the terms of their marketing authorisation. This argument is closely linked to the view of the European Feed Manufacturers' Federation (FEFAC) (2015) that, in order to combat AMR without endangering animal health, restrictions on the use of antimicrobials must be accompanied by research aimed at developing new treatments and reducing the need for antimicrobials.

With regard to marketing authorisations, one interviewee (INT7) commented that the VMP proposal would build on work done by the EMA. In relation to restrictions on off-label use, the same interviewee (INT7) remarked that the EMA had been working towards restrictions in this area. Finally, on labelling, the interviewee (INT7) mentioned that the EMA had done work to ensure more detailed and in many cases more restrictive labelling of veterinary antimicrobials (such as third- and fourth-generation cephalosporins), for example, proscribing use for group treatment or use before other treatments have been tried and failed.²⁶

The proposal on medicated feed also covered authorisation requirements. It introduced, *inter alia*, a ban on preventative use of antimicrobials via medicated feed;

²⁶ Several referral procedures regarding veterinary medicines containing CIAs were launched and/or completed under Article 35 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products, and these resulted in product documentation being amended to reflect measures to prevent the development of AMR.

requires diagnosis-based prescription for antimicrobials; and limits prescription validity and the duration of a treatment. Views on the proposal on medicated feed were similarly split between different stakeholder groups. Similar to the proposal on veterinary medicines, BEUC argued that the wording of the proposal on medicated feed was too vague and that it should be tightened to make a clear distinction between prophylactic and metaphylactic use of medicated feed (BEUC 2015). Moreover, BEUC (2015) urged the European Commission to consider an outright ban on the use of antimicrobials in feed, citing poor efficacy as the basis for such a ban. BEUC's stance was countered by organisations representing the agricultural and food industries, who argued that certain elements of the European Commission proposals were too restrictive. For example, FEFAC stated that the proposed maximum levels of 'carry-over' (defined as 'the transfer of traces of an active substance into non-target feed' (EC 2014d)) were too low, as some degree of carry-over was unavoidable (FEFAC 2015). Copa-Cogeca supported this view, stating that the proposed 1 % limit on carry-over went 'beyond the principle of proportionality and technical feasibility' (Copa-Cogeca 2015) — a view that was shared by some academic studies (e.g. Stolker et al. 2013).

4.1.2.2. There was an overall decrease in the volume of antimicrobials sold for animal consumption annually in the EU

Data on sales of antimicrobials for use in animals highlighted significant variation between countries in terms of consumption trends, but showed an overall improvement in the EU. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project collects information on antimicrobial medicines sold for use in animals across the EU/EEA. This type of information can aid in the identification of possible risk factors that could lead to the development and spread of antimicrobial resistance in animals.

The 2015 ESVAC report provides sales data at package level for antimicrobial veterinary medicinal products in 26 EU/EEA countries²⁷ in 2013 (representing approximately 95 % of the food-producing animal population in the EU/EEA). In 24 of 26 countries, a legal basis existed for the national competent authority to request data on sales or prescriptions of veterinary antimicrobial agents from the distributors of such products, while in two countries (France and the Netherlands), data were provided voluntarily to the national competent authority (EMA 2015a).²⁸

Large differences in total sales between countries were observed throughout the period 2011-2013 based on milligrams per population correction unit (PCU) (Figure 7). In 2013, for example, Norway had the lowest sales, at 3.7 mg/PCU, whereas Greece had the highest sales, at 425.8 mg/PCU.²⁹ A decrease in sales of 7.9 % (mg/PCU) was observed on average across all countries during the period of the Action Plan for which

²⁷ Sixteen of the countries obtained the data from wholesalers, six from marketing authorisation holders, two from both wholesalers and marketing authorisation holders, and two from pharmacies. In some countries, feed mills provided the data on sales of premixes used in medicated feed.

²⁸ These data were intended to be comparable because they were gathered according to ESVAC guidelines in each country. No consumption (actual use) data were provided, and the report did not include information on the types of animal (species) present in each country.

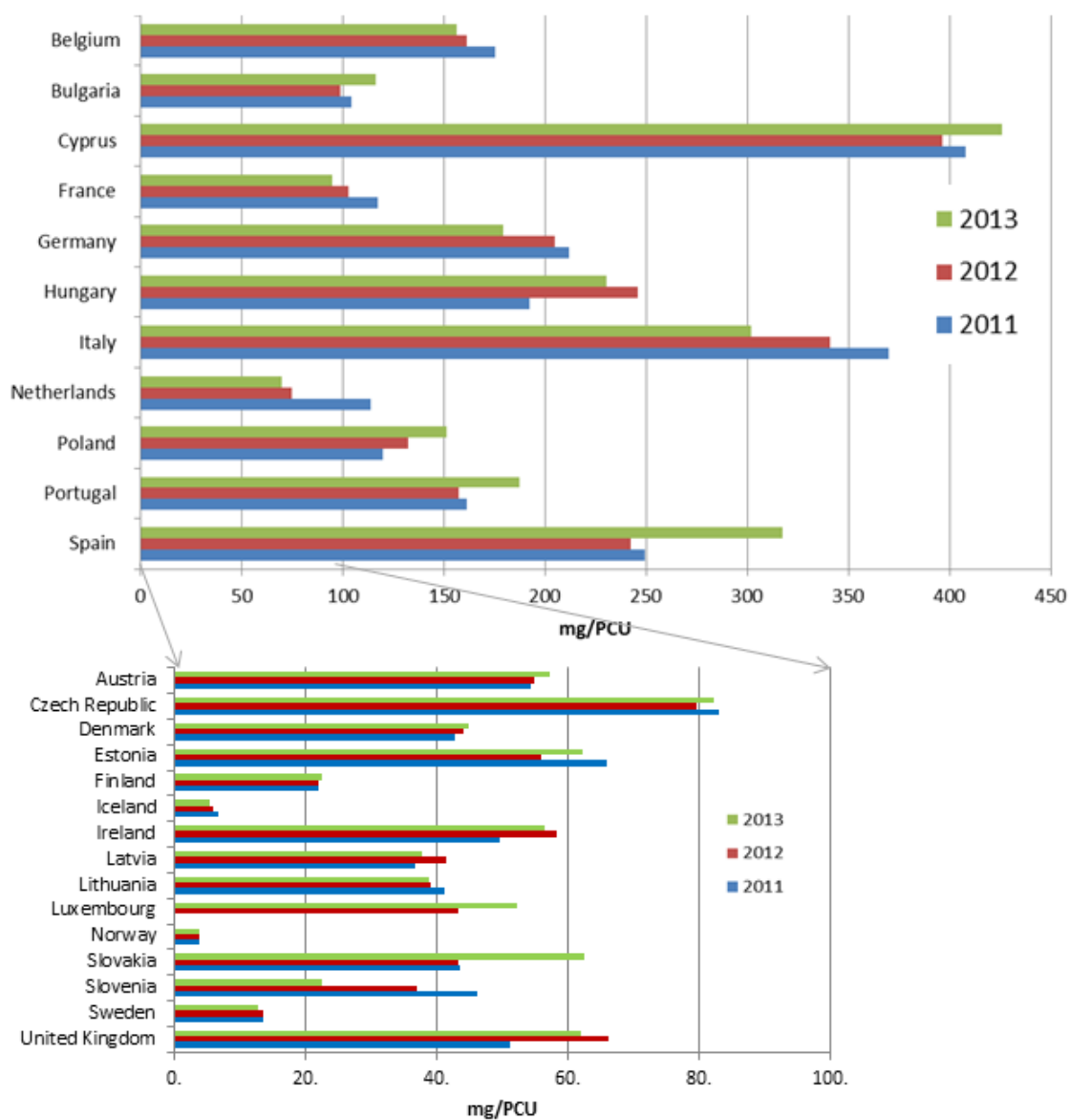
²⁹ PCU is used to normalise the sales data for the size of the country-level animal population using an estimated weight at treatment of livestock and slaughtered animals. Concerns were raised by some interviewees about the reliability of the PCU. As noted in a recent ESVAC report, 'It should also be emphasised that the PCU only represents a technical unit of measurement and not a real value for the animal population that could potentially be treated with antimicrobial agents' (EMA 2015c, 119). The unit may not accurately capture (i) the consumption occurring in that Member State or (ii) variation in usage across species, composition of animal populations or drug potency.

data were available (2011-2013) (Figure 8). A decrease in sales of more than 5 % (range: 5.6-51 % mg/PCU) was observed for 11 of the 23 countries. An increase in sales (in mg/PCU) of more than 5 % (range: 5.4-21 %) for the period 2011 to 2013 was observed for 6 of the 23 countries (EMA 2015a).

High levels of variation persisted between countries, with average sales as much as 100 times higher in high-sales countries than in low-sales countries. The variation has been attributed to a combination of factors, including differences in the composition of animal populations, differences in the antimicrobial treatments used and differences in dosage and length of treatment. The 2015 ESVAC report provides explanations from Member States for these trends (EMA 2015a). The explanations include increased awareness about AMR, the presence of campaigns to encourage responsible use, restrictions on use (including the introduction of usage targets) and shifts in animal demographics.

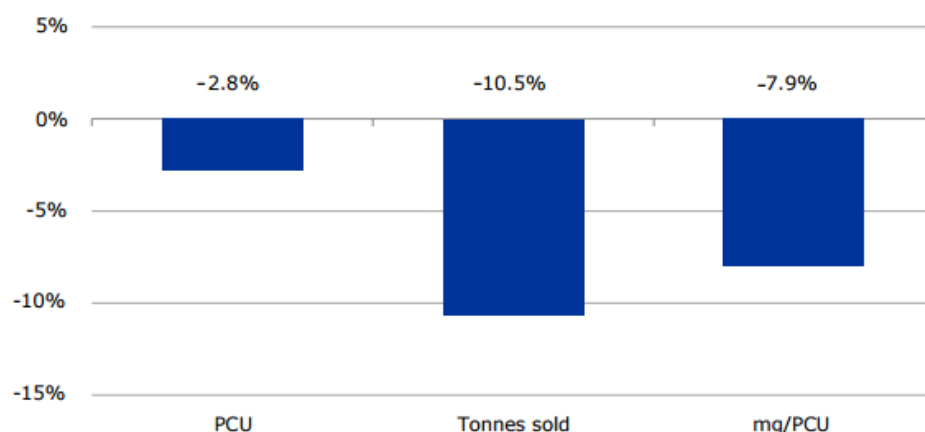
Figure 7: Total sales of veterinary antimicrobial agents for food-producing species, including horses, in mg/PCU, in 26 EU/EEA countries (2011-2014)

Countries with sales greater than 100 mg/PCU per annum (top) and less than 100 mg/PCU per annum (bottom)



Source: ESVAC database.

Figure 8: Percentage change in PCU; tonnes sold; and sales of veterinary antimicrobial agents for food-producing species, including horses, in mg/PCU, aggregated by 23 EU/EEA countries (2011-2013)³⁰



Source: EMA 2015a.

The 2015 ESVAC report states that there was not yet enough evidence to conclusively link awareness campaigns to the reductions observed. An interviewee (INT21) from a non-EU country also commented on the difficulty of attributing the reduction in overall consumption of veterinary antimicrobials to specific interventions, but suggested that action plans and information campaigns have played a role. The interviewee gave examples of information dissemination by the European Commission, as well as by the World Organisation for Animal Health (OIE), the FVE and the European Federation for Animal Health and Sanitary Security. This view was shared by an independent expert (INT7), who stated that the reduction in consumption could not be attributed only to one action, but to a broader increase in political will to combat AMR, which had resulted in action plans being produced by groups including doctors and veterinarians. Another interviewee (INT4) from an EU-level body attributed reduced consumption to specific actions, including national policies (particularly in the Netherlands and France), as well as the EC Action Plan, which, the interviewee stated, had helped to raise awareness of AMR in veterinary medicine.

4.1.3. Support for research and innovation funded research projects, promoted public-private collaboration and facilitated international coordination, although barriers to innovation in veterinary antimicrobials persisted

Two objectives and three actions of the Action Plan related to research and development, with a focus on developing new, effective antimicrobials or alternatives for treatment and on reinforcing research and innovation. This section discusses the effectiveness of each.

4.1.3.1. Support was provided for collaborative research and development to bring new antimicrobials to patients

The EC Action Plan included an action to promote collaborative research and development efforts to bring new antimicrobials to patients (action 6). The action encompassed three main aspects: improving efficiency of research and development through open sharing of knowledge, establishment of adequate market and pricing conditions for new antimicrobials and implementing fast track procedures for the

³⁰ The 23 countries included are: Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Italy, Ireland, Latvia, Lithuania, the Netherlands, Norway, Portugal, Poland, Slovenia, Spain, Sweden and the United Kingdom. Bulgaria, Luxembourg and Slovakia were excluded due to missing data.

marketing authorisation of new antimicrobials. The Action Plan described specific initiatives and mechanisms that would be the focus of activities under this action, and support for R&D was provided through the programmes outlined.

The Action Plan led to the successful establishment of a framework agreement on a long-term perspective on public-private partnerships, with the New Drugs for Bad Bugs (ND4BB) programme being the flagship example (INT1, INT5, INT8, INT9, INT10, INT11, INT27).³¹ ND4BB is part of the public-private partnership Innovative Medicines Initiative (IMI) and a joint programme between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). It involves small, medium and large pharmaceutical companies; academia; regulatory authorities; and patient groups (IMI 2010a).

The ND4BB initiative focuses on creating a more sustainable European clinical investigator and laboratory network and using that network for improved and more efficient clinical development of new antibiotic drug candidates (EC 2015c). Its aims also include advancing understanding of the underlying science, progressing promising novel hit or lead molecules into early clinical development, and developing options for novel economic models of antibiotic R&D and responsible use of antimicrobials.

Seven ND4BB programmes were launched between 2013 and 2015, with expected completion dates ranging from 2017 to 2021. The ND4BB programmes focus on the development at different stages of new antimicrobials to combat specific infections or types of bacteria (e.g. iABC, TRANSLOCATION, ENABLE and COMBACTE-CARE), the development of viable business models for antibiotic development (Driving reinvestment in research and development and responsible antibiotic use — Drive AB), and the establishment of pan-European networks for clinical investigation (COMBACTE) and surveillance (COMBACTE-MAGNET).³²

ND4BB progress during the evaluation period included consideration of new business models and approaches for funding antibiotic development (INT1, INT9, INT10, INT11, INT16), particularly through the DRIVE-AB project (INT1, INT16). ND4BB was highlighted by one interviewee (INT16) as an example of an emerging consensus on the need to address the economic issues surrounding new drug development.

An aim of the Action Plan was to introduce mechanisms, such as the ND4BB programme, to reduce inefficiencies in antibiotics R&D and strengthen Europe's capacity to do clinical research in this area by improving data sharing among companies. While the concept of data sharing and information exchange between companies and the private sector is central to the ND4BB programme (TRANSLOCATION 2016), the evidence is mixed about actual improvements in open sharing of knowledge under ND4BB. A representative of a company involved in developing new antimicrobials (INT1) noted the importance of the ND4BB in achieving

³¹ One interviewee representing an EU-level stakeholder organisation (INT21) noted that one of the benefits of ongoing EU-funded projects had been the establishment of international and interdisciplinary networks which (directly or indirectly) focused on AMR. Another interviewee (INT11) commented that Europe was in a unique position to engage in these activities due to the amount of money made available for antibiotic development.

³² The full programme names are as follows: Inhaled antibiotics in bronchiectasis and cystic fibrosis (iABC), Molecular basis of the bacterial cell wall permeability (TRANSLOCATION), European Gram-negative Antibacterial Engine (ENABLE), Driving re-investment in R&D and responsible antibiotic use (DRIVE-AB), Combatting Bacterial Resistance in Europe (COMBACTE), Combatting Bacterial Resistance in Europe — Carbapenem Resistance (COMBACTE-CARE), and Combatting Bacterial Resistance in Europe — molecules against Gram negative infections (COMBACTE-MAGNET). Further details on the characteristics of each programme are provided in Appendix M.

this aim and considered the ENABLE project to be a clear example of ongoing open sharing of knowledge, while a representative of the European Commission (INT5) highlighted the central database set up as part of the TRANSLOCATION project as an example of open knowledge sharing.³³

Another interviewee involved in research (INT11) agreed that the industry had made great strides in sharing research through the ND4BB programme, but felt that it was still not operating on a fully open sharing platform given that the IMI is a closed consortium and data generated from some programmes is restricted to consortium partners (e.g. ENABLE and TRANSLOCATION) (a view shared by INT20). The idea that the data sharing happening through the IMI projects could be made more open to the wider research community was also raised by participants at the second stakeholder workshop. Dissemination of research results could be further enhanced through data standardisation and uniform data capture mechanisms; long-term curation of datasets and better tools for their interrogation; and publications, workshops, conferences and other fora to facilitate and encourage personal relationships (INT27).

The development of new antimicrobials is also one of the foci of IMI2 (IMI 2014). This initiative is a continuation of the IMI, from 2014 to 2020, extending its scope beyond pharmaceutical companies to the participation of other science industries that were not always involved in biomedical research (e.g. information technology). AMR is listed as one of 12 health priorities to be addressed by IMI2 in its strategic research agenda; accordingly, IMI2 focuses on the following four research axes that are common to all 12 priority areas: target validation and biomarker development; adoption of innovative clinical trial paradigms; innovative medicines and patient-tailored adherence programmes (IMI 2014). The explicit inclusion of AMR in IMI2's strategic documentation (in contrast with the first IMI) was a direct impact of the Action Plan, according to an interviewee from a European-level public body (INT5).

It is too early to draw conclusions as to whether the longer-term objectives of these activities have been achieved; visible impact in the form of new antimicrobials and more companies developing new products and strategy in the field take years to materialise.³⁴ But in terms of intermediate outcomes, survey results help to indicate in how far progress was achieved during the timeframe of the Action Plan. In particular, only 5 % of 93 respondents indicated that improved efficiency of research and development through open sharing of knowledge had been achieved; 25 % indicated that this had been partly achieved, while 26 % indicated that no progress had been made. Among 50 respondents to the question on whether progress could be attributed to the Action Plan, 36 % indicated it could and 22 % that it could not (the rest were unsure).

In support of efforts to develop new antimicrobials, the EMA developed two guidance documents to support the underlying regulatory framework. First, an updated version of guidelines for pharmaceutical companies active in the area specifies how studies assessing the risks and benefits of new medicines, including antimicrobials, should be conducted (EMA 2011). Second, its accompanying addendum provides a discussion of existing options for the clinical development of new antibacterials, focusing on agents effective against multi-resistant pathogens (EMA 2013a). As a follow-up, the EMA hosted a workshop in November 2013 on how to best use existing legislation in bringing new antimicrobials to patients (EMA 2013b).

³³ The TRANSLOCATION project involves an information centre for the sharing of previously confidential data being provided by companies that are members of EFPIA, and the project is intended to support dissemination of information from all of the ND4BB projects (IMI 2010a).

³⁴ Other studies, for example, by Hanney et al. (2015) and Morris et al. (2011), have shown that biomedical research takes years to decades to produce new drugs and other forms of treatment.

Survey respondents were less supportive, however, of the idea that adequate market and pricing conditions for new antimicrobials had been achieved: 36 % indicated that no progress had been achieved in this area, 11 % indicated that some progress had been achieved, and just one respondent indicated that the objective had been achieved. Scepticism regarding progress in the area of new drug development was reiterated during the first stakeholder workshop, which included a relatively small number of participants from research organisations and companies involved in medical innovation (see Appendix H for a list of participants). At the first workshop, the area of new drug development stood out as the one where participants felt that the situation had worsened and the Action Plan had not made a positive contribution, but at the second workshop, which involved more representatives active in R&D, participants emphasised that research and innovation requires a long time to achieve progress compared with other areas. Participants at the first workshop did agree with the intentions expressed in the Action Plan in this area and thought that action at the EU level may have stimulated interaction and collaboration between public authorities and small and medium-sized enterprises (SMEs), and this progress was confirmed by participants at the second workshop.

4.1.3.2. Incentives have been identified but have not yet improved the development of new antimicrobials in veterinary medicine

The EC Action Plan noted that the development of new antimicrobials for use in the veterinary sector may be hampered by uncertainties regarding future regulatory regimes and their requirements, and action 7 focused on efforts to analyse the need for new veterinary antibiotics (EC 2011). As one part of this action, the Commission requested scientific advice from the EMA (EC 2012) on how human and animal health may have been impacted by antimicrobial use in the veterinary context and measures to manage the risk to humans. The first part of the advice, which covered old antibiotics to treat infections with multi-resistant bacteria in humans (in particular colistin and tigecycline), was delivered by the EMA's Antimicrobial Advice ad hoc Expert Group (AMEG) in July 2013. The remainder of the scientific advice, including on new antimicrobials, was delivered in 2014. As a follow-up to the delivery of the advice, the Commission organized a workshop dedicated to its analysis in November 2015, bringing together more than 70 representatives of EU agencies, Member State authorities and other stakeholders (EC 2015g). The workshop was cited by one survey respondent as an efficient example of exchanging stakeholder views.

The Commission legislative proposal on veterinary medicinal products, published in September 2014, identified incentives intended to stimulate the development of new antimicrobials for use in the veterinary context. Incentives included an extension of protection periods for technical documentation (with an initial period of 14 years).

These developments under the Action Plan only occurred in the last 2-3 years of the plan, however, and were unlikely to have yielded results during the evaluation period. Indeed, reflecting on conditions for the development of new veterinary antimicrobials, approximately half of Member State and stakeholder survey respondents (52 %, or 46 out of 89) indicated that there were either barriers to innovation or a lack of incentives to promote innovation in the area. Only two respondents indicated that there were incentives that promote innovation.

The challenges were emphasised by one interviewee involved in research into new antimicrobials (INT1), who felt that there were no incentives for companies that were not currently focused on veterinary medicine to try to enter that market. The interviewee suggested applying similar measures to those in place in the human medicine context, citing funding for innovation and initiatives such as Drive AB as examples of ways that the development of a viable business model for R&D on new veterinary antimicrobials had been facilitated. A similar point was made by an interviewee working in drug innovation (INT16), who did not observe any progress in incentivising innovation in veterinary antimicrobials or reducing the barriers

acknowledged in the Action Plan in this area (i.e. uncertainty about whether new substances would be authorised for veterinary use). However, the consultee felt that there had been good discussion of appropriate use of antimicrobials in the veterinary sector, placing Europe ahead of the rest of the world.

Participants in the first stakeholder workshop also indicated that overall either there had been no progress or the situation had worsened and the Action Plan had not had an impact in this area. Several participants suggested that the way the Action Plan's goals were formulated did not support progress because the call to analyse the need for new antimicrobials in veterinary settings, as opposed to a call to develop new antimicrobials, may have conveyed less urgency with respect to animal health.

Incentivising the development of treatments to reduce antimicrobial use in the veterinary sector was the focus of case study 7, on Norway's aquaculture industry (Appendix N), where the development of effective vaccines for bacterial infections enabled a drastic reduction in the use of antimicrobials — 99 % in the period 1987 to 2007. Norway used 'creative governance' of its veterinary pharmaceutical industry to incentivise private sector involvement in the vaccines. In exchange for a 3 % tax on all sales of veterinary vaccines, the Norwegian Veterinary Institute offered free evaluation of vaccine prototypes if the results were made public. This approach lessened the risk to be taken by veterinary pharmaceutical companies and thus reduced a major barrier to the development of new vaccines. This example illustrates an approach to the much wider challenges being faced across the EU and globally — one which may be informative for future efforts.

- 4.1.3.3. Additional measures to support research brought important progress in the coordination of research at national level, but there may be a need to broaden the scope of topics supported

Under action 11, the Action Plan set out to reinforce and coordinate research efforts by (i) promoting research to understand AMR and pathogen-host interactions; (ii) promote research on diagnostic tools, vaccines and other preventive measures; (iii) support the launch of a JPI on AMR, which would coordinate research activities at national level; (iv) support an investigation into why some countries have high levels of AMR and are high users of antimicrobials; and (v) contribute to a global mapping of AMR.

The European Commission used its flagship research funding instruments, FP7 and Horizon 2020, to support AMR research. Fifteen research projects addressing AMR were launched in 2013 with the support of FP7 funding as a direct response to the Action Plan (EC 2013a). The projects focused on a range of topics, including developing alternatives to antimicrobials; preventative measures, such as vaccinations; and improved use of existing antimicrobials.^{35,36} Horizon 2020 also prioritised AMR and had selected 145 AMR-related projects for funding at the time of the evaluation, including the development of vaccines against tuberculosis (TBVAC 2020 and EMI-TB) and Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) (EAVI2020) (EC 2015d,h).

In 2015, a Horizon Prize of €1 million was launched to award the development of a new, rapid, point-of-care diagnostic test targeting patients with upper respiratory tract infections (ongoing at the time of the evaluation). The expected outcome was that this

³⁵ As discussed in Chapter 5, an analysis of EU research funding during 2007-2013 (excluding IMI) found that about two thirds of funding supported projects related to developing new antibiotics and alternatives to antibiotics (Kelly et al. 2015).

³⁶ One of the explicit goals of this set of projects was to further stimulate innovative small and medium-sized enterprises.

test would enable prompt identification of patients who could be treated without antimicrobials.

InnovFin ID is another financing instrument used to support AMR research, which was launched in June 2015 by the European Investment Bank and the Commission. The instrument was expected to provide funds to applicants who cleared the pre-clinical stage in the development of novel interventions for infectious diseases, such as vaccines, drugs, medical and diagnostic devices or novel research infrastructures (European Investment Bank 2016).

The EU set up and supports the Joint Programming Initiative on AMR (JPIAMR) through a Coordination and Support Grant (JPIAMR 2013a). The initiative is an integral part of the European Commission's research efforts, as envisaged in the Action Plan (action 11) and demonstrated by the Commission's financial commitment (INT5). It brings together 22 countries (including 15 EU Member States)³⁷ and aims to overcome the fragmentation of existing national research programmes by pooling the resources of its members and avoiding duplication of effort (JPIAMR 2013b). JPIAMR has issued two transnational calls for AMR research (ibid.), indicating that it had begun to deliver on this objective during the evaluation period (JPIAMR 2013a). It also supported an analysis of AMR research funding that has been provided by the JPIAMR and the EU over the period 2007-2013 (Kelly et al. 2015). The WHO also recognised the importance of the JPIAMR strategic agenda, referencing it as an initial framework for a global AMR research agenda (WHO 2015a). A WHO representative commented that the JPIAMR had been a successful initiative for achieving collaboration and coordination in research and that its strategy represented a strong basis for developing a global research agenda (INT24).

Work also progressed on other actions under action 11 during the evaluation period (INT5). This included progress in addressing imprudent use of antimicrobials in human medicine,³⁸ including through the Antimicrobial resistance and causes of non-prudent use of antibiotics in human medicine (ARNA) research project by the Netherlands Institute for Health Services Research (NIVEL 2016). Use of antimicrobials and their effectiveness was addressed through the Genomics to Combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE) research project. A global mapping of resistance was initiated in collaboration with the WHO. The global mapping initiative, led by the WHO and the European Commission, primarily provided European data and identified ways that the information could further support the global mapping effort, but a WHO representative (INT24) said that a global mapping had not yet been achieved.³⁹

³⁷ The seven non-EU participating countries were Argentina, Canada, Israel, Japan, Norway, Switzerland and Turkey. One interviewee (INT20) highlighted the global dimension of JPIAMR and suggested that there was good progress in the EU in demonstrating how to take leadership to tackle issues at a global level.

³⁸ One interviewee (INT16) suggested that more could be done to understand the high use in certain countries. The interviewee pointed out that, while ECDC did very good monitoring, this effort did not translate into high-quality policy recommendations. This may have been largely due to the fact that the ECDC sees its mandate as being limited to gathering and publishing data.

³⁹ Another example of a coordination of effort supported by EU action was the use of the European Innovation Partnership Agricultural Productivity and Sustainability to establish a focus group on how to reduce the use of antibiotics in pig farming. The final outcome of the group's activity was a report with a series of recommendations for the promotion of underused best practices, future field testing and future sustainable research and innovation in the following areas: general animal health welfare; alternatives to antibiotics; and attitudes, information and human behaviour (EIP-Agri 2014).

All of these activities occurred relatively late in the evaluation period, and it was generally too early to assess whether they had been effective. This judgement was supported by comments made by participants at the second stakeholder workshop and by Member State and stakeholder survey respondents. In the survey, around one third (from 28 % (37 out of 132) to 34 % (46 out of 135)) of respondents indicated that it was too early to say whether each of the activities were effective.

About 30-40 % of survey respondents felt that activities to support various aspect of research had been at least partly effective; a large proportion (at least 20 % in each area) were unsure. Less than 5 % of respondents felt efforts had not been effective, with the exception of two areas (development of diagnostic tools and vaccines). In their comments, some respondents advocated for a wider scope of activities. Some of their suggestions reflected the idea that more work in vaccines and diagnostics is needed, while others included research and development on reducing the need to use existing antimicrobials, alternative treatments, manufacturing drugs in the EU to secure supply, and AMR as an occupational health issue.

These comments, particularly on the need for research on diagnostics, vaccines and alternatives to antibiotics, were echoed by participants at both stakeholder workshops and by interviewees. A research interviewee (INT8) felt that the development of diagnostic tools was the weakest aspect of AMR R&D work, and diagnostics for use in animals were identified by two international experts (INT17, INT20) as a research area in need of greater attention. Still, three interviewees working in research (INT9, INT10, INT27) acknowledged the contribution of FP7 and IMI funding in the development of diagnostic tools, vaccines and other preventative measures. One interviewee working in research (INT11) indicated that there had been a lot of progress in supporting the understanding of the basic mechanisms of AMR and the development of diagnostic tools.

Participants in both stakeholder workshops generally agreed that while it may have been worthwhile investing more resources in research on new types of drugs and treatments, this area had not received nearly as much attention as research into traditional antibiotics. Participants at the second stakeholder workshop acknowledged that one objective of the Action Plan was to develop effective antimicrobials or alternatives for treatment of infections, but indicated that it was not clear what was meant by 'treatment alternatives' and commented that more work should be done in some areas, including diagnostics (particularly point-of-care diagnostics), vaccines, social factors that influence how antimicrobials are prescribed and used, and ways to treat mild infections that would not require antibiotics. While FP7 and IMI projects were initiated to develop non-classical drugs or treatments, overall, the workshop participants observed that research in these areas remained fragmented.

4.2 Extent to which actions aimed at containing the risks of spreading AMR were effective

Evaluation question 4: *To what extent have the actions aimed at containing the risks of spreading AMR been effective?*

This evaluation question addressed the contribution of the Action Plan to ongoing efforts to contain the spread of AMR and the risks thereof. Judgement criteria and evaluation indicators for this evaluation question covered the following areas: the legal basis for containing AMR in the veterinary sector, bilateral and multilateral commitments to contain the risks of AMR, surveillance and monitoring systems, AMR awareness, and trends in indicators of resistance.

4.2.1. The proposed animal health law is expected to provide the basis for monitoring of animal pathogens

The Commission adopted a proposal in 2013 for a new Animal Health Law as envisaged under action 5 of the Action Plan. It was intended to provide the legal framework in support of the 2007 EU Animal Health Strategy and has the following aims:

- '[E]nsure a high level of public health and food safety by minimising the incidence of biological and chemical risks to humans;
- '[P]romote animal health by preventing/reducing the incidence of animal diseases, and in this way to support farming and the rural economy;
- '[I]mprove economic growth/cohesion/competitiveness in assuring free circulation of goods and proportionate animal movements; [and]
- '[P]romote farming practices and animal welfare which prevent animal health related threats and minimise environmental impacts in support of the EU Sustainable Development Strategy.'

To achieve these aims, the proposal includes a suite of measures. Among the most important provisions, it provided a prioritized list of diseases likely to have a significant impact and set out notification and surveillance responsibilities. It includes a regulatory framework for vaccination and required Member States to have contingency plans in place for certain diseases. Furthermore, it specifies the rules regarding the approval, registration, movement and traceability of animals. It introduces standards for the importation and exportation of animals, products of animal origin and germinal products and for procedures to be followed in cases of emergency.

The proposal was undergoing the ordinary legislative procedure at the time of the evaluation: political agreement was reached among the European Parliament, Council and Commission in June 2015. Among the provisions of the agreed upon text, both the European Parliament and the Council would be involved, in consultation with EFSA, in establishing and maintaining a list of potentially dangerous diseases. The agreed upon rules also specify the responsibilities of stakeholders, such as veterinarians, farmers and traders, in ensuring good animal health (Council of the EU 2015; EC 2015f; Paulsen 2015). The Animal Health Law was adopted in March 2016 (Council of the EU 2015).

Nearly three quarters of Member State and stakeholder survey respondents reported being aware of the Commission's proposal for the new Animal Health Law (73 %, or 66 out of 90; figures were similar for Member State and stakeholder respondents). These respondents were invited to comment on its potential overall effectiveness and, specifically, on the effectiveness of the inclusion of a legal basis for monitoring AMR in animal pathogens. The majority of respondents (73 %) indicated that the law had the potential to be effective: 80 % of Member State respondents (36 out of 45) and 66 % of stakeholder respondents (29 out of 44) identified at least some potential for effectiveness. None of the Member State and only three of the stakeholder respondents reported that it had 'little to no potential to be effective'. Regarding the inclusion of a legal basis for monitoring AMR in animal pathogens, 77 % of respondents indicated that this had at least some potential to be effective. Six respondents explicitly commented on the potential effectiveness of monitoring resistance in animal pathogens, which was supported by four of the interviewees (INT2, INT3, INT4, INT7). One survey respondent commented that the law could be effective in particular in relation to multi-resistant microbes. Two respondents identified potential for effectiveness because the law was compulsory for all Member States.

4.2.2. Bilateral and multilateral commitment mechanisms for the prevention of AMR were strengthened and linked to the Action Plan

The EU undertook several initiatives in the area of multilateral and bilateral cooperation. The progress report on the EC Action Plan against AMR (EC 2015c) showed that the EU engaged with partners including the WHO, OIE, China, the United States, and Russia, as well as developing countries.

The EC Action Plan and several associated initiatives⁴⁰ fed in to the development of the WHO's global Action Plan on AMR (WHO 2015a). The draft global Action Plan was prepared with the support of the Strategic and Technical Advisory Group on AMR, which had a European Commission representative as a member (WHO 2015a). In the text of the plan, the JPIAMR was explicitly mentioned as a potential framework for further development of a global strategic AMR research agenda. In addition, the EU's monitoring systems were discussed in the context of a WHO/Europe meeting on implementing the Global Antimicrobial Resistance Surveillance System (GLASS), where it was noted that the EC Action Plan's objectives are well aligned with the WHO global Action Plan, including multi-sectoral action with a 'one health' approach and AMR surveillance (WHO/Europe 2016e). GLASS aims to support the WHO's objective to establish a global standardised approach to the collection, analysis and sharing of data. It would build on such networks as the European Antimicrobial Resistance Surveillance Network (EARS-Net) and the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network, established as an effort between the ECDC and WHO to align monitoring standards between EU and non-EU countries in Europe.⁴¹

At the regional level, collaboration was strengthened between WHO/Europe and the Commission. AMR was identified as an area for cooperation through the 'Health Security Roadmap' (WHO/Europe 2015). This cooperation included the implementation of the WHO/Europe strategy on AMR, the Communication from the Commission on a Community Strategy against AMR (COM(2001) 333) and the EC Action Plan (WHO/Europe 2012). The ECDC and WHO/Europe established a technical collaboration focusing on AMR surveillance, consumption of antimicrobials and HAIs and conducted several joint missions in both EU/EEA and EU enlargement countries aimed at discussing AMR and HAI issues (WHO/Europe 2015). The cross-national ECDC activities served as a model for the international system that the WHO wants to establish (INT15).

A WHO interviewee suggested, however, that the EU could encourage European countries (both within and outside the EU) that are facing similar challenges to work more together to address AMR and that the WHO could also be approached to provide support. While there is significant disparity across the EU, some Member States (particularly newer ones) face similar challenges to non-EU countries in the WHO European region (e.g. EU candidate countries) (INT24). Benchmarking studies across Member States could help countries identify which areas they need to focus on (Workshop 2).

In addition, the Commission funded the European Reference Laboratory for AMR (EURL-AR) which collaborated with WHO on several issues pertaining to AMR monitoring in the food chain. EURL-AR supported the activities of the Global

⁴⁰ These include the JPIAMR, European Commission-funded research, EARS-Net, and Healthcare-associated Infections Surveillance Network (HAI-Net).

⁴¹ CAESAR was designed to be fully compatible with EARS-Net reporting standards. In addition to ensuring data comparability and compatibility, this also facilitated the transition for EU candidate countries upon accession from the WHO-administered system (CAESAR) to a system administered by ECDC (EARS-Net).

Foodborne Infections Network as well as those of the WHO Advisory Group on Integrated Surveillance of AMR (AGISAR) (EC 2015a).

Multilateral cooperation included EU engagement with the OIE through the organisation of a 2013 global conference on the use of antimicrobials for animals, participation in the elaboration of OIE standards on AMR, updating the chapters on AMR in the OIE Terrestrial Animal Health Code, and setting up a global database on antimicrobials use relevant for animals (EC 2015b; OIE 2015a). A Global Task Force on AMR was established as a cooperative effort between the WHO, the Food and Agriculture Organization of the United Nations (FAO) and OIE following the World Health Assembly in 2014 (EC 2015a).

The Commission and EMA, EFSA and ECDC also worked towards the creation, adoption and implementation of the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (CAC/GL 77-2011), part of the Codex Alimentarius, which informed risk analysis and provided direction for mitigating the dangers to human health associated with foodborne AMR (TATFAR 2014). The Commission and its agencies also participated in 2015 in Codex work on the review of the *Code of Practice to Minimise and Contain AMR* (CAC/RCP 61-2005) and *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (Codex Alimentarius Commission 2005, 2011; EU 2015).

The Commission supported the Organisation for Economic Co-operation and Development (OECD) in its activities on AMR research, focusing on assessing the economic impact of AMR and accompanying policy options (EC 2015b). An OECD representative explained in an interview that final agreement between the OECD and the European Commission on AMR-targeted work was expected in early 2016 (INT13). This bilateral collaboration was expected to focus on assessing the effectiveness, including cost-effectiveness, of policies aimed at tackling AMR. At the time of the evaluation, the final report from this bilateral agreement was planned for early 2018, with an intermediary output in 2017. The OECD interviewee also acknowledged the Action Plan's contribution, noting that it had prompted work with the OECD by highlighting the need for the Commission to find and put in place effective and cost-effective actions (INT13).

Bilateral achievements include the continuation of TATFAR, a partnership centred on collaboration between the United States and the EU. TATFAR was set up in 2009 with a focus on three areas: (i) appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, (ii) prevention of both healthcare- and community-associated drug-resistant infections and (iii) strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed through intensified cooperation. TATFAR began with 17 recommendations for future collaborations between the United States and the EU (CDC 2015), and its first mandate, running from 2011 to 2013, focused on the implementation of the agreed upon recommendations.

At the end of this period, following assessment on the progress achieved and the remaining needs, the mandate of TATFAR was extended for an additional two-year term. Over the course of the second mandate, TATFAR continued to address 15 recommendations, but it discontinued work on two previous recommendations.⁴² The new mandate also led to the creation of a new recommendation for collaboration to identify gaps in understanding the impact of antimicrobial use in animals and the risks of AMR for humans (CDC 2015).

⁴² These were recommendation 10, on developing consensus on evaluation tools for hospital infection control programmes, and recommendation 11, on developing a transatlantic strategy to facilitate vaccine development for HAIs.

The TATFAR progress report (2014) concluded that the taskforce had contributed to an increase in information exchange, identification of best practices and development of peer relationships. TATFAR recommendations were recognised and taken into account by other recent global initiatives, such as the Group of Seven (G7) initiative on AMR (Federal Ministry of Health (Germany) 2015). Interviews, however, indicated that there were mixed views of TATFAR's progress. One interviewee representing the pharmaceutical industry noted the small contribution TATFAR had made and stressed the slow pace of harmonisation in two directions: (i) medical acronyms and (ii) agreed upon primary endpoints for different diseases in the United States and the EU, leading to different clinical developments and hurdles in licensing for the same product in the two regions (INT6).⁴³ Another interviewee representing the pharmaceutical industry indicated that TATFAR had not produced tangible results (INT16).

By contrast, an expert from academia (INT18) stated that TATFAR had provided a good framework for collaboration between the EU and the United States. An interviewee from a European agency (INT23) stressed the benefits of sharing experiences and the potential for developing methodologies to enable global comparisons, in addition to EU-level comparisons. Moreover, according to this interviewee, TATFAR had produced important reports, for example, regarding the revision of guidelines on the requirement for clinical trials to authorise new human antimicrobials. The interviewee explained that some of the guidance was a direct result of recommendations from TATFAR. TATFAR was cited by one European Commission interviewee (INT12) as an important AMR coordination mechanism. Another interviewee (INT5) identified the importance of continuous communication on the topic of transatlantic action with the United States, through which the EU intends to boost the pipeline for antimicrobials and provide information to researchers.

The EU also engaged with the Russian Federation and China. The dialogue on communicable diseases established in 2009 placed AMR on the agenda of bi-annual meetings with the Russian Federation (Directorate General for Health and Consumers of the European Commission & Ministry of Health and Social Development of the Russian Federation 2009). In 2013, two seminars were held in China on AMR, following a 2012 visit to China of the Commissioner for Health and Consumers that established AMR as an area of cooperation (EC 2015c). The Commissioner undertook another visit to China in autumn 2015 (EC 2015j), and, as indicated in the Action Plan Road Map, comparative policy studies were conducted (EC 2015i). One example was a comparison of AMR policies in the EU and China, which built on an EU and China seminar held in 2013 (van Dissel et al. 2015). The objectives of the study were set by the EU-China Trade Project. The JPIAMR is another example of a mechanism for addressing AMR with third countries.

4.2.3. Surveillance systems improved in both human and animal medicine, and these improvements were linked to the Action Plan

European surveillance systems on antimicrobial use and resistance in humans and animals rely on four principal components: ESAC-Net for use in humans, ESVAC for use in animals, EARS-Net for resistance in humans, and compulsory reporting to EFSA of resistance in food-producing animals and food.

4.2.3.1. ESAC-Net improved the scope of data collected on antimicrobial consumption in humans

ESAC-Net is a Europe-wide network of national surveillance systems providing independent reference data on antimicrobial consumption in humans across Europe. Responsibility for ESAC-Net was transferred to ECDC in 2012 from the European AMR

⁴³ Key area III of TATFAR pertained to strategies to improve the pipeline of new antibacterial drugs for use in human medicine.

Surveillance System, which was managed by the University of Antwerp (EC 2015c; ECDC 2014a). The network collects and analyses data from the community sector (i.e. primary care), where most antimicrobials are consumed in Europe, as well as from the hospital sector.

ESAC-Net data were analysed and published in three annual reports during the evaluation period.⁴⁴ The third report was published in September 2014 for data collected in 2012 and included consumption data reported to ECDC by all 28 EU Member States and two EEA non-EU countries (Iceland and Norway) (ECDC 2014b). This represented an improvement over the first annual report which included data from 24 Member States and the same two EEA non-EU countries (ECDC 2013).⁴⁵

Improvement in the scope of data collected was also observed during this period. For example, in 2012, 25 countries reported consumption data on antimycotics and antifungals for systemic use in the hospital sector, whereas in 2010 only 17 countries reported these data. In all three years, only Denmark and Slovenia provided data on consumption by age group. The ECDC emphasised the importance of more countries providing stratified data by age and on the number of packages consumed to enable the identification of high consumers of certain antimicrobials in population subgroups (ECDC 2014b).

4.2.3.2. ESVAC supported improvements in harmonised reporting on antimicrobial sales for animals and the development of new or revised rules in many Member States

The ESVAC project was launched by the EMA in 2010 in response to a Commission request to harmonise the collection and reporting of data on the use of antimicrobials in animals, and it collects information on how antimicrobial medicines are used in animals across the EU/EEA (EMA 2015a). A standardised data collection protocol and common template which is now web-based (EMA 2015a) were developed by ESVAC to support the harmonisation of data collection processes across all Member States. This helped ensure that countries met a minimum set of standards and collected data in a consistent and harmonised manner, in order to produce reliable and credible cross-country comparisons. ESVAC's first annual report was published in 2011 (reporting 2010 data). The number of countries using the standardised data collection protocol to report national-level sales of antimicrobial medicinal products increased from 19 in 2010 to 26 in 2013 (the most recent year for which data are available), representing 95 % of the food-producing animal population in the EU/EEA (EMA 2015a). Case study 4 (Appendix N) explored ESVAC's evolution and concluded that the data it provided had been of critical importance to the identification of trends in antimicrobial consumption, both across the EU and within Member States, during the period of time since the Action Plan was launched.

However, Member State reporting was done on a voluntary basis, and one interviewee (INT19) considered a lack of formal legislative requirement to be a primary cause of persistent data gaps. The ESVAC surveillance system is being further strengthened through the legislative proposal on veterinary medicines, which provides for compulsory collection of data on sales and use of veterinary antimicrobials.

ESVAC had several achievements since the publication of its first annual report in 2011, which analysed existing data on national-level sales for the period 2005-2009 from countries with well-established surveillance systems. During the evaluation

⁴⁴ In addition to the annual reports, the ESAC-Net website provided access to the data for the period 1997-2014 through a bespoke, user-friendly, interactive database.

⁴⁵ The countries not included in the first annual report were Croatia, Cyprus, Romania and Slovakia. Croatia was not an EU Member State at that time.

period, ESVAC took steps to collect data by species as well as overall data on sales, the need for which is discussed in case studies 4 and 5 (Appendix N). ESVAC reporting and increases in ESVAC data coverage were noted by three interviewees (INT4, INT7, INT21) as an example of a positive development in monitoring efforts. One interviewee (INT21) commented on the improved collection and availability of data on consumption of veterinary antimicrobials, emphasising the importance of these data in highlighting concerns and informing decision-making on interventions to combat AMR.

In addition to supporting improvements in harmonised reporting, ESVAC supported the development of new or revised rules in many Member States, whereby distributors (drug sellers and wholesalers) of relevant antimicrobial products are legally required to report annual sales figures to the national competent authority. The data collected during the evaluation period represent overall sales by Member State and were published in five annual reports, complemented by an interactive online database. However, there is room for further improvement in that the data are presented in mg sales per PCU per Member State, which may not accurately capture (i) the consumption occurring in that Member State or (ii) variation in usage across species, composition of animal populations or drug potency (Section 4.1.2.2).

4.2.3.3. EARS-Net data quality improved, and Member States became better able to report comparable AMR data

EARS-Net is the primary EU surveillance system for AMR in humans. As with ESAC-Net, responsibility for managing the system was successfully transferred to the ECDC in 2010. The network collects and analyses data on AMR for bacteria and antimicrobial groups of public health importance, which serve as important indicators of the occurrence and spread of AMR in European countries. Analyses of these data during the evaluation period were presented by ECDC in annual reports, the first of which was published in 2010 and the most recent, in 2015. In 2015, most countries reported data for all bacteria and antimicrobial groups under surveillance (ECDC 2015a). This represented an improvement over previous years with respect to resistance of *Acinetobacter* and *Streptococcus pneumoniae*.

In the period 2009-2015, data quality improved and Member States became better able to report comparable AMR data. Factors influencing these improvements included (i) an increase in the number of participating laboratories; (ii) standardised breakpoints⁴⁶ for antibacterial susceptibility testing becoming more widely implemented; and (iii) a larger proportion of laboratories joining the annual EARS-Net external quality assessment exercise (ECDC 2015a).

4.2.3.4. Zoonoses data reporting improved through interagency collaboration

Directive 2003/99/EC on the monitoring of zoonoses — that is, infections that are transmissible between animals and humans — and zoonotic agents requires reporting countries to monitor and report to the Commission, and subsequently to EFSA, on AMR in zoonotic *Salmonella* spp. and *Campylobacter* spp. isolates from food-producing animals and food. EFSA and the ECDC analysed the information collected and published annual reports,⁴⁷ the first of which was published in 2011 using 2009 data

⁴⁶ Breakpoints used to define susceptibility and resistance to antibacterials are typically expressed in terms of concentration (in mg/litre or µg/ml) or a zone diameter (mm). An issue in the interpretation of ECDC data on antimicrobial resistance is that the breakpoints vary between countries, and in some instances even between laboratories in the same country.

⁴⁷ The data were collected from EU Member States and from Norway and Switzerland. In addition to data on resistance to antimicrobials by such organisms as *Salmonella* and *Campylobacter*, which may cause infectious diseases transmissible between animals and humans and which can be found in foods, data were also collected on antimicrobial resistance of indicator *Escherichia coli* and Enterococci, which usually do not cause disease in humans.

on 25 Member States (EFSA & ECDC 2011). The most recent report, published in 2016, used 2013 data from 28 Member States (EFSA & ECDC 2015).

A new legal framework for harmonised monitoring of AMR in zoonotic and commensal bacteria (Commission Implementing Decision 2013/652/EU⁴⁸) was created under action 10 of the Action Plan and came into force on 1 January 2014. Requirements were established for harmonised monitoring and reporting of the most relevant combinations of bacterial species and food-producing animal populations and foods from a public health perspective. The new legislation aims to ensure the comparability of results between Member States and between the human and veterinary sectors, although it was too early to identify any results from the new requirement during the evaluation period, because the most recent available data covered 2013.⁴⁹ Improvements in zoonoses resistance data over time were highlighted by ECDC and EFSA (2016); for example, 2014 was the first year that all Member States reported data on poultry and poultry meat at the level of bacterial isolates, enabling EU- and country-level analyses of resistance patterns.

As another indication of progress, in 2015, an interagency report jointly analysing AMR and antimicrobial consumption in humans and food-producing animals was produced by the ECDC, EFSA and EMA for this first time. It used data from 2011 and 2012 reported by EU Member States, Croatia, Iceland, Norway and Switzerland (ECDC, EFSA & EMA 2015). The analysis found that consumption was higher in animals than in humans overall, but that this varied across countries. It also found that for most combinations of drugs and species analysed, higher levels of resistance were positively correlated with antimicrobial consumption. However, there were limitations to the data and analyses due to differences in how the data were collected and reported. The report emphasises that the findings should be interpreted with caution and states that ongoing improvements will enable improved cross-analysis.

4.2.3.5. Improvements in surveillance systems could generally be linked to the Action Plan

Member State and stakeholder survey respondents commented overall on monitoring mechanisms for AMR and consumption in human and animal contexts during the evaluation period. The majority of respondents (ranging from 53.6 to 78.3 %, depending on the topic) thought that monitoring had improved in terms of data coverage across Member States, harmonisation of data across Member States and sustainability of surveillance. Assessments were least positive regarding sustainability of veterinary monitoring and surveillance of both antimicrobial use and antimicrobial resistance. More effective measures may have been needed to encourage action from Member States that were lagging behind, for instance in gathering data for monitoring and surveillance in both the human and animal contexts (INT7, INT17).

When asked whether these developments could be attributed, at least partly, to the Action Plan, about half of human health survey respondents agreed for both surveillance of antimicrobial use in humans (52 %, 37 out of 71) and resistance in humans (51 %, 36 out of 71). Only two and three respondents in each area,

⁴⁸ Repealing Decision 2007/407/EC and 2013/653/EU.

⁴⁹ Commission Implementing Decision 2013/652/EU of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (EC 2013b). The decision built on previous EFSA work on developing technical recommendations for the harmonisation of monitoring and reporting of resistance, as put forward in a report on monitoring and reporting resistance in *Salmonella*, *Campylobacter* and indicator commensal *Escherichia coli* and *Enterococcus* spp. bacteria transmitted through food (EFSA 2014b) and in MRSA in food-producing animals and food (EFSA 2012).

respectively, did not think the Action Plan played a role in these developments. In their clarifying comments, seven respondents explicitly highlighted the activities of the ECDC in this area and its contribution to observed trends. Case study 5 (Appendix N) found that the Action Plan's call for better and more integrated surveillance and monitoring systems across Member States led to the development of interagency surveillance reporting in the EU, which combined data for animal and human use for the first time. But this case study also identified a need for species-specific data in animals and further integration of existing regulations.

Similar to the human health survey respondents, 61 % of respondents with expertise in animal health (52 out of 86) indicated that observed trends in the surveillance of antimicrobial use in animals could be attributed to the Action Plan, and a majority (57 %, 50 out of 88) shared that view with respect to surveillance of resistance in animals. As with the human health perspective, with the exception of two individuals, the remainder of respondents were unsure. The reasons for this assessment were similar to those offered by the human health participants: respondents highlighted EMA and ESVAC activities, and six highlighted the Action Plan as having a role in encouraging Member State action and improving the comparability and harmonisation of data in this area.

In assessing the Action Plan's contribution to the observed improvements, two interviewees (INT17, INT21) explicitly highlighted the 'one health' approach, which was, in their view, exemplified by the Commission's willingness to engage stakeholders and foster dialogue with relevant parties. Among other benefits, this resulted in progress in the area of harmonisation of surveillance data between human and animal contexts.⁵⁰ Interviewees also highlighted the role of ECDC as a strong contributor in this area (INT12, INT15)⁵¹ and acknowledged the role played by TATFAR in standardising measures between the EU and the United States (INT15).

One interviewee (INT12) noted persistent gaps in access to data on resistance in humans at the regional and local levels in some contexts and in the quality and coverage of data, which could differ depending on the micro-organism in question. *Campylobacter* was highlighted as an example of inadequate monitoring. In addition, the interviewee suggested that there was room for improvement in data collection on human health system stewardship. While some countries collected information on trends in clinical practice and its appropriateness, the stakeholder representative indicated that this should have been done more systematically at the EU level. Another interviewee (INT19) expressed concern that while monitoring had improved, its results had not always been acted upon.

4.2.4. There were some improvements in awareness of AMR and appropriate antimicrobial use among the general public

Eurobarometer surveys on AMR conducted in 2009 (TNS Opinion & Social 2010) and 2013 (TNS Opinion & Social 2013) enabled monitoring of trends in knowledge, perception and self-reported attitudes of Europeans towards antimicrobials.⁵² Reported

⁵⁰ Progress in harmonisation was also explicitly noted by two other interviewees (INT4, INT14). Speaking from the perspective of human health, one of them considered harmonization between the monitoring of human and animal use to be the Action Plan's main contribution, since other human health monitoring systems were largely in place before the Action Plan was adopted.

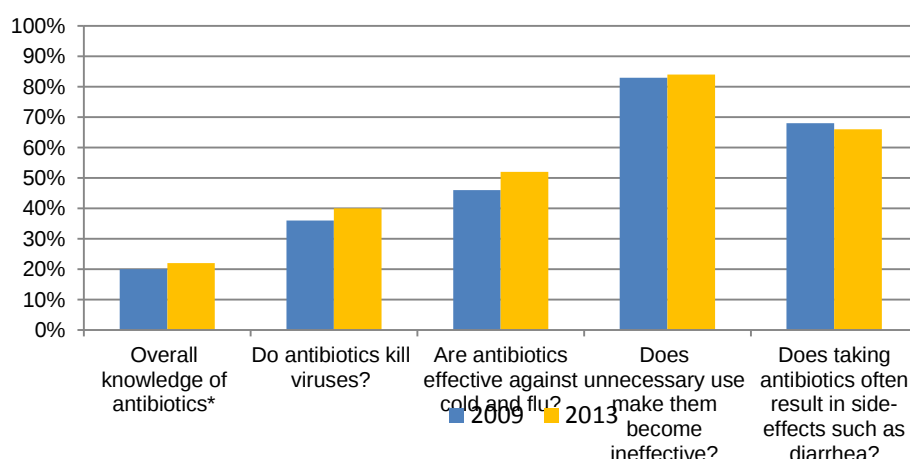
⁵¹ Two interviewees stressed the completion of the transfer of responsibility for human use and resistance data to ECDC, which collected and processed the information as part of its routine operations.

⁵² Some Eurobarometer data (from 2009) predate the existence of the EC Action Plan, and no new information or data were gathered on this issue in the context of this evaluation. No more recent data were available.

use of antimicrobials by Eurobarometer survey participants decreased between the two surveys (40 % in 2009, versus 35 % in 2013). ESAC data showed no overall reduction in actual use, however, which may be explained by the fact that self-reported and actual behaviours are not always consistent, with self-reported behaviours often overestimating more favourable behaviour.

The Eurobarometer survey results indicate improvements in knowledge about how to use antimicrobials and their effectiveness, but little change when it comes to understanding the secondary effects of antimicrobials and the fact that unnecessary use of antimicrobials makes them become ineffective. About half of Eurobarometer respondents in 2013 believed that antimicrobials are effective against viral infections, and overall knowledge about antimicrobials remained low, with only 22 % of respondents being able to give correct answers to four questions to test their knowledge of this issue (Figure 9). In addition, the 2013 Eurobarometer survey revealed significant variation in terms of reported usage of antimicrobials among Member States even though the differences between them decreased between 2009 and 2013. These results were inconsistent with the data analysed in Section 4.1.1, which found that differences had not decreased among Member States in the same period.

Figure 9: Proportion of correct answers to the Eurobarometer survey on knowledge about antimicrobials (2009 versus 2013)



Source: Data extracted from the 2013 Eurobarometer summary report.

* Percentage of respondents able to give the right answer to all four questions.

The Eurobarometer results also highlight variations in the effectiveness of awareness-raising campaigns. For instance, respondents from France, Belgium and Luxembourg were more likely to have been reached by awareness campaigns than those from Portugal, Hungary and Spain: only 12 %, 17 % and 20 % of respondents in these latter countries, respectively, could recall having received information, compared with 65 % in France (findings from case study 6 on French awareness campaigns are presented in Box 1). Those disparities were explained by a lack of a targeted approach in the way European and national awareness campaigns were designed, as reported in the 2013 Eurobarometer (TNS Opinion & Social 2013). Indeed, European Antibiotic Awareness Day (EAAD) campaigns were the responsibility of each Member State, and no standardized, EU-wide awareness programme existed at the time of the evaluation.

The 2013 Eurobarometer concluded that media and communications campaigns were successful overall in raising awareness, as exemplified by the fact that those who 'received information from media campaigns [were] more likely to be better informed than those who received advice from medical professionals' (TNS Opinion & Social 2013, 80). However, only 33 % of respondents received the information in 2013,

compared with 37 % in 2009, and just over one third (36 %) said that their views had changed because of the information received.

The link between national campaigns and positive outcomes in terms of awareness and stewardship was noted in the literature. For instance, Filippini et al. (2013) analysed 21 national campaigns and found a significant impact of national campaigns on antibiotic consumption, with a reduction in use ranging between 6.5 % and 28.3 % for the nine countries that implemented public campaigns from 1997 to 2007. There were limited data on national awareness campaigns for the period of the evaluation, with most studies predating the Action Plan or being too recent to provide results. A summary of available data on selected national campaigns is provided in Appendix M.

There are other limitations inherent in evaluating national campaigns. First, public health campaigns are under-evaluated (Latham et al. 2014) or only partially evaluated (Fuller et al. 2015) at Member State level. Also, potential unintended effects of the campaigns might not be explicitly identified (Huttner et al. 2010) and the reviews might lack transparency. In addition, evaluations are rarely able to rely on comparison or control groups in their attribution of effects and frequently take the form of pre-/post-observational studies. As such, the possibility of bias and confounding factors behind any observed effects cannot be discounted. Furthermore, the sustainability of awareness-raising actions can be questioned over the long term (Huttner et al. 2010).

Box 1: Success and challenges in French awareness campaigns (case study 6, Appendix N)

France ran an intensive annual public campaign, 'Antibiotics are not automatic' ('Les antibiotiques c'est pas automatique'), from 2002 to 2012, which aimed to educate caregivers and the public that antibiotics are not always necessary and which described their appropriate use. Another campaign, 'Antibiotics are not automatic for us either' ('Les antibiotiques pour nous non plus c'est pas automatique'), which extended to animal health, was launched in 2014 (it was not directly linked to the EC Action Plan).

- The human health campaign was praised in a formal evaluation for its scope (Huttner et al. 2010) and noted for its impact on antibiotic prescribing (WHO/Europe 2011b).
- The human health campaign was accompanied by a reduction in antibiotics consumption and the achievement of national targets to reduce antibiotic prescriptions, although an evaluation did not establish a causal link between the campaign and these outcomes (Sabuncu et al. 2009; Huttner & Harbarth 2009).
- The animal health campaign coincided with decreases in animal exposure to antibiotics and in sales of veterinary antibiotics in France, but it was difficult to establish a causal link because other initiatives were implemented in parallel (CS9-1 and CS9-2), the campaign had not been formally evaluated, and the impact of such campaigns on animal health was unknown (Lhermie et al. 2015).

Challenges identified include attributing changes in behaviour to the campaigns and difficulties in sustaining positive effects from such campaigns over time.

The French examples could provide helpful models for countries that have yet to implement campaigns, with appropriate adaptations for local contexts.

Although the majority of public campaigns were addressed to the general public, healthcare professionals were also targeted through educational material (Huttner et

al. 2010). Some successful campaigns, including the French campaign that is the subject of case study 6, adopted a multi-faceted approach targeting the general public and healthcare professionals at the same time (Huttner et al. 2013).⁵³ An individual interviewed in the context of case study 6 (Appendix N) suggested that there should be a special focus (e.g. an additional action in the Action Plan) on supporting national authorities in developing national awareness campaigns in the veterinary sector. However, the case study highlights that the impact of awareness campaigns on antibiotics consumption in the area of animal health is unknown (Lhermie et al. 2015).

The major awareness campaign at the European level is European Antibiotic Awareness Day. It was established on 18 November 2008 by the ECDC with a view to supporting the development of national awareness campaigns (Earnshaw et al. 2014). In 2013, the 677 articles published during a two-month period (in print or online) and referring to EAAD were estimated to have reached more than 67.9 million readers, a 12 % increase compared with 2012 (ibid.). Additionally, television messages were estimated to have reached an average of 14 million EU citizens each year, and among them an average of 1.5 million people working in the healthcare and medicine sectors in Europe.

The success of the European campaign was measured by the increased number of participating countries, which grew from 32 in 2008 to 43 in 2013. According to the ECDC, in 2013, 22 countries reported in an annual ECDC evaluation questionnaire that there had been a change in their country that could be attributed to the momentum created by EAAD (Earnshaw et al. 2014). Thus, Earnshaw et al. (2014) concluded that EAAD had been successful in supporting pre-existing national campaigns and fostering the development of new, but similar campaigns in countries with limited financial and political support. Individuals interviewed in the context of case study 6, on the French campaigns (Appendix N), perceived that EAAD had an impact on raising awareness among policymakers but that in order to reach the public, its messages should be simpler and more targeted to each Member State's specific context.

No formal evaluation of the overall impact of EAAD on antibiotic consumption and resistance had been performed at the time of the evaluation due to the heterogeneous implementation of national campaigns across EU countries, although some evaluations were undertaken at the Member State level. In 2013, an evaluation by Public Health England analysed the direct impact of EAAD in England and Wales and found a reduction in antibiotics prescriptions between 2008 and 2013, which could be attributed partly to the success of the initiative (Ashiru-Oredope & Hopkins 2015; Bhattacharya et al. 2014). In 2015, EAAD was incorporated into a World Antibiotic Awareness Week, which addressed the issue on a global scale.

In addition to raising awareness for patients and the general public, EAAD aimed to improve knowledge on the use of antibiotics for clinicians in both primary and secondary care (Leaper 2010; Bhattacharya et al. 2014; McNulty 2012). For instance, in the UK, EAAD 2013 was found to have a high level of engagement with professionals, with 91 % of healthcare organisations reported having activities planned in support of EAAD (Bhattacharya et al. 2014).

Awareness of national campaigns was high among survey respondents: 73 % (99 out of 135) Member State representatives and stakeholders were aware of AMR awareness campaign in their country.⁵⁴ When asked whether the Action Plan or other EU support

⁵³ Information on campaigns targeted at doctors and implemented by governments at the national level is presented in Appendix M.

⁵⁴ Human health respondents were more likely to recall an awareness campaign than were animal health respondents (83 %, or 38 out of 46, versus 66 %, or 41 out of 62).

played a role in the decision to implement these activities, the majority of respondents (61 %, 62 out of 102) responded in the affirmative. Of these, 14 respondents explicitly mentioned ECDC activities or EAAD as factors supporting the campaigns in their respective Member States.

4.2.5. EU trends in antimicrobial resistance varied over time

Since 2011 in the EU, the prevalence of resistance to antimicrobials occurring in bacteria of major importance to human health and in zoonotic bacteria has varied considerably, depending on the organism and antimicrobial group under consideration. Thus, it was not possible to identify clear trends in the level of AMR for the EU overall during the period of the evaluation.⁵⁵

The ECDC reports annually on resistance to antimicrobials for five bacteria of major public health importance (ECDC 2015a). Table 8 provides a summary of these data for the years 2011-2014 and highlights 10 cases in which the EU/EEA population-weighted mean resistance to antimicrobials increased during the period in question. For example, in the case of *Escherichia coli*, a statistically significant increase was observed in the percentage of invasive isolates with resistance to third-generation cephalosporins, from 9.6 % to 12 %, and in the case of *Klebsiella pneumoniae*, the percentage increased from 23.6 % to 28 %.

In seven of the bacterium-antimicrobial group combinations examined in the data, there was no statistically significant change in resistance levels between 2011 and 2014. For example, resistance of *Escherichia coli* to Aminopenicillins, Fluoroquinolones, Aminoglycosides and Carbapenems remained steady, although there were significant differences in the resistance of *Escherichia coli* to each antimicrobial. For example, resistance to Carbapenems was only 0.1 %, compared with resistance to Aminopenicillins, which was 57.1 %. Finally, there were three cases in which antimicrobial resistance declined — resistance of *Staphylococcus aureus* to meticillin (MRSA) and resistance of *Pseudomonas aeruginosa* to fluoroquinolone and to aminoglycoside (ECDC 2015a).

⁵⁵ These data should be treated with caution due to limitations acknowledged by ECDC. For example, there were differences in the sample sizes used in testing for resistance between countries, and the way in which resistance was defined (the 'breakpoint') also varied between countries and individual laboratories.

Table 8: EU-level trends in resistance in bacteria of major public health importance

	EU population-weighted mean resistance (%)				Statistically significant trends
	2011	2012	2013	2014	EU trend 2011-2014
<i>Escherichia coli</i>					
aminopenicillins	57.6	57.2	57.5	57.1	None
fluoroquinolones	22.4	22.2	22.4	22.4	None
third-generation cephalosporins	9.6	11.9	12.7	12	Increase
aminoglycosides	9.6	10.4	9.9	9.8	None
carbapenems	<0.1	0.1	0.2	0.1	None
fluoroquinolones, third-generation cephalosporins and aminoglycosides	3.8	4.9	4.6	4.8	Increase
<i>Klebsiella pneumoniae</i>					
fluoroquinolones	24.5	24.1	28.2	27.4	Increase
third-generation cephalosporins	23.6	24.6	29.1	28	Increase
aminoglycosides	20.1	21.3	23.7	23.1	Increase
carbapenems	6.0	6.4	8.4	7.3	Increase
fluoroquinolones, third-generation cephalosporins and aminoglycosides	16.7	17.4	20.1	19.6	Increase
<i>Pseudomonas aeruginosa</i>					
piperacillin + tazobactam	16	16.4	16.3	16.9	Increase
fluoroquinolones	22.1	20.8	20	19.4	Decrease
ceftazidime	12.8	13.3	12.3	13.1	None
aminoglycosides	16.7	18.4	15.8	14.8	Decrease
carbapenems	16.8	17	17.5	18.3	Increase
three or more of the above antimicrobial groups	14.1	13.5	13	13.3	None
<i>Staphylococcus aureus</i> (meticillin-resistant <i>Staphylococcus aureus</i> is known as MRSA)					
meticillin	18.6	18.6	18.1	17.4	Decrease
Enterococci					
aminoglycosides	33.9	29.1	30.8	28.8	None
vancomycin	6.2	8.1	8.9	7.9	Increase

Source: ECDC 2015a.

Note: The EU population-weighted mean excludes countries not reporting data for all four years. Insufficient data were available for the calculation of EU mean resistance for *Acinetobacter* and *Streptococcus pneumoniae* due to missing data for some years and some countries (e.g. for *Acinetobacter*, suitable data were collected in 25 countries in 2014, in 23 in 2013, but in fewer than 15 in 2011 and 2012).

Data on zoonoses and resistance in zoonotic agents are collected by EFSA and ECDC (EFSA & ECDC 2015, 2016). Of 13 groups of human zoonotic agents reported on by EFSA and ECDC, *Campylobacter* and *Salmonella* represented the majority of reported cases of gastrointestinal bacterial pathogens in all years of the Action Plan so far. In 2014, for example, the number of confirmed cases of human campylobacteriosis was 236 851 (71 cases per 100 000 population), and the number of confirmed cases of human salmonellosis was 88 715 (23.4 cases per 100 000 population). In contrast,

fewer than 7 000 cases of the third most common zoonosis, yersiniosis, were reported in 2014.⁵⁶

The most recent available data on resistance in zoonotic agents are from 2014, and these focus on poultry (namely, broiler chickens, laying hens and fattening turkey); data from pigs and cattle were reported in 2015 but were unavailable at the time of the evaluation. Member States are legally required to monitor and report on AMR in zoonotic and commensal bacteria under Commission Implementing Decision of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (2013/652/EU). Overall, the report found resistance to common antimicrobials (e.g. ciprofloxacin) was observed frequently in *Campylobacter* from humans and animals. High to extremely high resistance was observed in samples from broilers and humans. Resistance to common antimicrobials (e.g. tetracyclines, sulphonamides and ampicillin) and multidrug resistance were also frequently detected in *Salmonella* from humans and poultry. However, resistance rates varied widely across Member States. Data covering the period 2008 to 2014 were available for some Member States, depending on the species and drug of interest. A combination of increasing and decreasing trends was observed in different Member States and for different drug and species combinations.

4.2.5.1. A similar level of variation in levels of AMR in bacteria of major public health importance was observed in individual Member States

In addition to significant variation across the EU depending on the bacterium and antimicrobial group, there was considerable variation in resistance in bacteria of major public health importance across individual countries. For example, using the data collected annually by the ECDC on resistance to antimicrobials among five bacteria of major public health importance, rates of MRSA varied in 2014 between 0.9 % in the Netherlands and 56.0 % in Romania. This reflected a more general pattern of lower resistance percentages in countries in northern EU countries and higher percentages in southern and eastern Europe. The ECDC reported that these differences were most likely related to differences in antimicrobial use, infection control and healthcare utilisation practices in these countries (ECDC 2015a).

The data showed considerable variation not only between countries in the level of resistance of key bacteria of public health importance to antimicrobials, but also in the change in resistance since 2011 (ECDC 2015a) (Table 9).

⁵⁶ The study team attempted to draw broad insights into trends over time since the launch of the Action Plan, but these comparisons must be treated with caution because monitoring and surveillance schemes for most zoonotic agents were not harmonised among Member States, the data sampling may not have been informed by standard statistical techniques and not all countries reported data in every year. Furthermore, other factors, such as the time of year when the data collection took place, would likely impact on the results (e.g. infections in some cases are known to be more prevalent in poultry during the summer than during the winter).

Table 9: Member State-level trends in resistance in bacteria of public health importance (2011-2014)

	EU trend	Countries with upward trend	Countries with downward trend
<i>Escherichia coli</i>			
Aminopenicillins	None	LT, LU, BG	FI, DK, NL, CZ, HU
Fluoroquinolones	None	SE, BE, PT, EL, IT	DK, AT, DE, NL
Third-generation cephalosporins	Increase	SE, BE, FR, DE, IE, SI, CZ, PT, EL, IL, BG	DK, AT, DE, NL
Aminoglycosides	None	SE, CZ, HR, IE, SK, BG	NL, MT
Carbapenems	None	ES	None
Fluoroquinolones, third-generation cephalosporins and aminoglycosides	Increase	SE, FR, BE, UK, IE, HR, CZ, SK, IT, SI, BG	DK, LV
<i>Klebsiella pneumoniae</i>			
fluoroquinolones	Increase	FI, UK, IE, BE, ES, FR, MT, IT	DK, AT, HU, LT, CZ, EL
third-generation cephalosporins	Increase	SE, UK, IE, ES, FR, MT, PT, CZ, IT, RO	DK, AT, HU, LT, EL
aminoglycosides	Increase	FI, IE, ES, FR, MT, IT, CZ	NL, HU, LT, EL
carbapenems	Increase	FR, DE, HR, PT, ES, BG, IT	CY, EL
fluoroquinolones, third-generation cephalosporins and aminoglycosides	Increase	UK, IE, FR, MT, IT	NL, HU, LT, EL
<i>Pseudomonas aeruginosa</i>			
piperacillin + tazobactam	Increase	HU, SI, PT, IT	FR, RI
fluoroquinolones	Decrease	None	DK, AT, BE, DE, FR, SK
ceftazidime	None	SI, PT, HU, HR, IT	FR, EL
aminoglycosides	Decrease	None	DE, AT, MT, FR, SK
carbapenems	Increase	DE, HU, SK	EL
three or more of the above antimicrobial groups	None	SI, HU	AT, FR
<i>Staphylococcus aureus</i> (meticillin-resistant <i>Staphylococcus aureus</i> is known as MRSA)			
Meticillin	Decrease	DK, SI	UK, DE, LU, BE, FR, IE, IT, PT
Enterococci			
aminoglycosides	None	BE, AT	FR, EL, DE, CZ
vancomycin	Increase	DK, HU, IT, SK, HR, BG, UK, IE	FR, BE, DE

Source: ECDC 2015a.

Note: Data not available for *Acinetobacter* and *Streptococcus pneumoniae*.

In the seven bacterium-antimicrobial group combinations where there were no statistically significant time trends for the EU overall, a number of countries within the EU nevertheless experienced a significant increase or decrease in resistance. For instance, while the resistance of *Escherichia coli* to Aminopenicillins, Fluoroquinolones, and Aminoglycosides remained steady across the EU on average, in each of these three cases, a statistically significant upward trend was identified in at least three countries (e.g. Lithuania, Luxembourg and Bulgaria in the case of Aminopenicillins), which was offset by a statistically significant downward trend in at least five countries (e.g. Finland, Denmark, the Netherlands, the Czech Republic and Hungary in the case of Aminopenicillins).

Similarly in cases such as MRSA, where there was a decrease in resistance in the EU overall, there were some countries that experienced the opposite trend — for example, rates of MRSA increased in Denmark and Slovenia. The only cases where no increase in resistance was observed in any Member State was resistance of *Pseudomonas aeruginosa* to fluoroquinolones and aminoglycosides (in both cases there was also a decrease in resistance in the EU overall).

4.2.5.2. Rates of healthcare-associated infections remained stable during the evaluation period

Data on HAIs in individual Member States indicate that infection rates were stable over the evaluation period. Evidence on the prevalence of HAIs was obtained from the HALT surveys (see Section 4.1.1.4). In 2013, the crude prevalence⁵⁷ of long-term care facility residents with at least one HAI was 3.4 % (ranging from 0.4 % in Croatia to 7.1 % in Portugal) (ECDC 2014a). This represents an increase on the 2010 figure, which was 2.4 % (ranging from 0.0 % in Cyprus to 7.4 % in Portugal). In 2010 and 2013, the main HAI groups were respiratory tract infections (33.6 % in 2010 and 31.1 % in 2013), urinary tract infections (22.3 % in 2010 and 31.1 % in 2013) and skin infections (21.4 % in 2010 and 22.8 % in 2013).

While these data indicate that there was little change in HAIs in EU long-term care facilities since the Action Plan was launched, differences in the way the data were collected in 2010 and 2013 mean that comparisons between years should be treated with caution (e.g. it is possible that fewer cases were detected in 2010 due to underreporting of signs/symptoms by local staff members) (ECDC 2014a). Furthermore, the national representativeness of the data is poor, and countries with larger numbers of participating LTCFs did not use a representative sampling methodology (ECDC 2014a).

Evidence on HAIs is also available from ECDC surveillance surveys of surgical-site infections (SSIs), which were a common cause of HAIs in patients who had undergone surgery. The most recent data available, from 2012, involved 19 surveillance networks in 16 countries and included 422,201 surgical operations from 1,332 hospitals (ECDC 2014f). According to analyses undertaken by ECDC, statistically significant decreasing trends in SSIs were observed during the period 2009-2012 following caesarean section and laminectomy, and statistically significant increasing trends were observed after colon surgery. No statistically significant trend was observed for the cumulative incidence of SSIs in coronary artery bypass grafting, cholecystectomy, hip prosthesis and knee prosthesis. In line with the evidence from the HALT PPS data, the evidence suggests that the number of HAIs remained relatively steady. As with other survey data, the comparisons must be treated with some caution, not least since post-discharge surveillance methods and practices differed considerably between countries (ECDC 2014f). Also, since the most recent available data related to 2012, shortly after

⁵⁷ Crude rates provide data covering the entire population, without any reference to subgroups and without any adjustment for possible contributing variables.

the Action Plan was launched, more recent follow-up data would have been required in order to assess the impact of the Action Plan.

4.3 Extent to which coverage of actions across different services within the Commission were effective at capturing the holistic approach

Evaluation question 5: *To what extent has the coverage of actions across different services (DGs) within the European Commission been effective in capturing the holistic approach and delivering results?*

This evaluation question addressed the extent to which the Commission captured and delivered on a holistic approach to addressing AMR. The Action Plan states that AMR 'cannot be tackled through isolated, sectoral efforts' (EC 2011, 4).

The judgement criterion for this question was whether AMR-related actions were being carried out across the relevant European Commission DGs in accordance with the 'one health' approach, and whether they were joined up and coherent, with communication occurring across DGs. The associated evaluation indicators focused on whether the actions in the Action Plan covered the areas required for taking a holistic approach and whether responsibility for actions in the Action Plan was allocated to appropriate DGs, with no gaps identified. Indicators also assessed evidence that DGs successfully carried out the Action Plan actions in their remit and that Action Plan actions supported the 'one health' concept.

4.3.1. 'One health' aspects of the Action Plan were achieved within the Commission and more widely, although this was not always visible to those outside EU institutions and agencies

Overall, the Action Plan achieved a holistic or 'one health' approach simply through the existence of a single policy instrument that addressed both animal health and human health aspects of the AMR problem.⁵⁸ Improved comparability of animal and human data was identified as one of the main ways in which the Action Plan had enabled progress that would not otherwise have been achieved (INT14). Case study 5, on the effect of the Action Plan on work across animal, food and human settings and the prevalence of drug resistance in *Salmonella* in the EU (and reporting of this resistance) (Appendix N) showed that the Action Plan promoted collaboration and coordination across European agencies and the animal and human health sectors. On this basis, it can be said that the Action Plan made important progress towards the 'one health' approach.

Commission and European agency representatives reported that the Action Plan encouraged interactions among Commission DGs responsible for animal health, human health, agriculture, and research and development and that it resulted in coordination across DGs and agencies.⁵⁹ The Commission succeeded in encouraging dialogue across sectors, which should lead to actions being taken to tackle problems in a way that takes into account the challenges and needs across sectors, as well as improving the comparability of data gathered across sectors (INT21). Individuals responsible for health and agriculture were also reported to have worked more collaboratively on AMR, instead of blaming one another for problems (INT17, INT23). Addressing issues in both areas together was critical for accurately assessing risk (INT23).

⁵⁸ Representatives of the European Commission; European and international agencies and organisations; and independent consultants and researchers, namely, INT2, INT3, INT5, INT6, INT12, INT13, INT14, INT15, INT21.

⁵⁹ INT5, INT12, INT17, INT21, INT23.

Important examples of cross-sector collaboration occurred with regards to monitoring and surveillance. Harmonisation of human and veterinary surveillance under action 10 was identified as a particularly important outcome of the Action Plan (INT7, INT13). Case study 5 showed that the Action Plan call for better and more integrated surveillance and monitoring systems across Member States led to the development of interagency surveillance reporting in the EU, which combined usage and resistance data from the animal and human contexts for the first time. An interagency report, produced by the ECDC, EFSA and EMA was commissioned by the European Commission in 2012 to provide data on the relationship between the consumption of antimicrobial agents and the occurrence of AMR in both humans and food-producing animals (ECDC, EFSA & EMA 2015). The report, released in 2015, combined data across five surveillance programmes, run by EARS-Net, ESAC-Net, FWD-Net, the Scientific Network for Zoonosis Monitoring Data, and ESVAC. Also, in line with a sub-action on establishing harmonisation between human and veterinary surveillance to allow data comparison under action 10, the ECDC launched a protocol for harmonized monitoring of AMR in human isolates of *Salmonella* and *Campylobacter*; it included guidance on how to compare data obtained from humans and animals (ECDC 2014g).

The case study on cross-sector work to address *Salmonella* prevalence cited the new Animal Health Law⁶⁰ as an example of, *inter alia*, a cross-sectoral approach to the enforcement of the appropriate use of antibiotics, as this law established the responsibility of authorities and stakeholders to protect animals, humans and the environment from drug-resistant pathogens, and it further clarified possibilities and obligations to ensure appropriate monitoring, surveillance and early detection of pathogens across sectors.

International collaboration was another way in which the Action Plan was successful at capturing the 'one health' approach through EU collaboration with the OIE, FAO and WHO, which enabled third countries to also be included in Action Plan activities, thus helping to tackle AMR issues at the global level (INT21).

EU-funded calls for research were yet another outcome of the Action Plan exemplifying a holistic approach, as they encouraged collaboration between researchers involved in animal health and human health, who had previously not been encouraged to work together (INT5).⁶¹ Other actions that were identified as concretely linking the animal and human health sides were the inclusion of explicit objectives on antibiotics for human use in the veterinary medicines legislation review under action 2 (INT12).

While the Action Plan helped to promote a more integrated, or 'one health', approach to AMR within the Commission and between the Commission and agencies, this integration was not fully apparent to stakeholders outside the Commission. Participants in the first stakeholder workshop representing organisations involved in animal and human health issues commented that there was a need for a more overtly 'one health' or holistic approach⁶² in the Action Plan because, while animal health and human health elements were present in the Action Plan, they were addressed separately. One participant observed that it was as if the human and veterinary sides

⁶⁰ The law was adopted by the Commission in May 2013, was undergoing procedural steps during the evaluation and was adopted in March 2016.

⁶¹ Specific funded projects identified were EvoTAR (Evolution and Transfer of Antibiotics Resistance), which started in October 2011 and thus was not a result of the Action Plan (although the interviewee explained it was related to a call designed with the development of the Action Plan in mind), and EFFORT, which started in December 2013.

⁶² As mentioned elsewhere, in general, participants linked the 'one health' concept and a holistic approach, indicating they perceived them to be closely related.

were 'two different worlds'. This view was also expressed in interviews (INT15, INT17, INT24). However, one agency representative (INT23) observed that, although achieving 'one health' in practice was quite difficult and required continuing effort, the way the plan was constructed appropriately brought together the actions of the different agencies and the Commission.

Comparing the responses from survey respondents with stated expertise in human health, animal health or both, we note that a majority of human health experts (71 %, or 36 out of 51) and animal health experts (69 %, or 44 out of 64) said that the holistic approach was captured,⁶³ but among respondents with stated expertise in both human and animal health only 36 % agreed that the holistic approach was captured (10 out of 28), while 39 % (11 out of 28) said it was not captured.

Member State survey respondents were more positive about whether the Action Plan captured a holistic approach than were those representing stakeholder organisations, thereby reflecting that those involved with policy implementation have a different perspective than do policy users. Among respondents representing Member States, 78 % (53 out of 68) said the holistic approach was captured and 10 % (7) said it was not, whereas 49 % (37 out of 75) of respondents representing stakeholder organisations indicated that the holistic approach was captured and 28 % (21) indicated that it was not.

As an example, one interviewee (INT15) discussed the issue of whether certain new classes of antibiotics should have been restricted for use only by humans to preserve their effectiveness, and said there was poor appreciation from the veterinary side about the concerns being raised in human medicine, and *vice versa*. The interviewee indicated that there was a need for the various actors involved to improve their understanding of the others' perspectives, and that this would have required creating more venues for discussion.⁶⁴ This comment is consistent with comments made by participants at the first stakeholder workshop that the workshop had been valuable because it provided an unusual opportunity for stakeholders involved in animal and human health issues to interact.

One reason for this difference in perception between those working with and within the Commission and its agencies compared with those outside the EU institutions and bodies be that, while the Action Plan clearly aimed to capture the 'one health' approach (for instance by referring explicitly to this approach in its text), most of its actions fell under specific sectors. As a result, external stakeholders might not have been aware of cross-sector collaboration taking place among the Commission's DGs and the agencies, and they would not have experienced such collaboration themselves.

4.3.2. The Action Plan covered sectors relevant for AMR, but the environment and international cooperation were identified as areas that should have received greater emphasis

While there was no formally agreed upon definition of what constituted a holistic approach to AMR, AMR strategies and action plans developed by other countries and international bodies indicate the sectors that may be considered necessary to achieve such an approach. These areas are, broadly, human and veterinary medicine (including hospitals, medicines agencies, food chain safety, pharmacy, and monitoring and surveillance); environment; and research and innovation. The sectors identified in

⁶³ 16 % were unsure in each group.

⁶⁴ A workshop held by the European Commission on 26 November 2015 was held to discuss, *inter alia*, the same issue that was raised by this interviewee (EC 2015g).

the Action Plan itself as being among those relevant to AMR consist of a similar set of areas: medicine, veterinary medicine, animal husbandry, agriculture, environment and trade (EC 2011).

The actions of the Action Plan explicitly addressed the sectors identified as relevant to tackling AMR, including medicine related to human health (actions 1, 4 and 9), veterinary medicine and animal husbandry (actions 2, 3, 5 and 10), and medicine/veterinary medicine related to antibiotics development for humans and animals (actions 6 and 7). Agriculture was addressed through the connection to farm animal husbandry. In addition, some Action Plan actions were more cross-cutting, with potential relevance for multiple sectors. They addressed research and innovation (action 11), international cooperation (action 8) and public awareness about AMR (action 12).

The objectives also cut across sectors, with four objectives — ensuring appropriate use, prevention of infections, development of new antibiotics, and improving monitoring and surveillance — being relevant and involving actions for both the animal and human health sectors. The three other objectives — reinforcing research and innovation, international cooperation, and improving education and training — also had the potential to cut across sectors. International cooperation in particular consisted of cross-sectoral cooperative activities, while the reinforcement of research and innovation involved funding for research related to animal health, human health and the environment.

Action plan action 8 included one sub-action expressly related to the environment: to 'initiate cooperation on reduction of the environmental pollution by antimicrobial medicines particularly from production facilities' (EC 2011, 11). Under the Action Plan, a report on the risks of environmental effects from medicinal products (including antimicrobials) was carried out for the Commission (Mudgal et al. 2013). A strategic approach for action on pharmaceuticals in the environment (e.g. the pollution of drinking water) is expected by 2016, to be finalised in late spring 2017 (EC 2015c). The strategic approach should be followed, where appropriate, by proposals for measures two years following finalisation, in accordance with Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. The case study on impacts of cross-sector work on the prevalence of *Salmonella* in the EU (Appendix N) found that there were environment-related policies under development during the evaluation period.

Nevertheless, environmental issues were included to a greater extent and/or in a more cross-cutting way in several Member States' action plans or strategies, including those of Germany, the Netherlands, Norway and Switzerland. The WHO global Action Plan also highlighted a knowledge gap in this area, and it set out an action to develop standards and guidance about reducing risks of antimicrobial agents and residues in the environment (WHO 2015a).

Consultations undertaken for the evaluation identified limited emphasis on the environment in the Action Plan.⁶⁵ For example, environmental issues were identified in 6 of the 19 open-text responses to the question 'How could the EC Action Plan be made more holistic?' Commission representatives indicated that they were aware there may be a need for a greater focus on the environment. Representatives from DG ENV did not play a central role in the development and implementation of the Action Plan (INT7).

⁶⁵ INT7, INT15, INT18, INT19, INT23.

The JPIAMR named the environment as one of its six priority topic areas in its strategic research agenda (JPIAMR 2013b). The JPIAMR strategy stated that there is a need to assess how pollution in the environment (in potable water, water in the environment, food and soils) by antibiotics, antibiotic residues and resistant bacteria contribute to the spread of AMR, and to develop strategies to minimise that contamination (JPIAMR 2013b). The JPIAMR plans to issue a call in 2016 for research related to the transfer of resistance among humans, animals and the environment (INT5).

The importance of international cooperation was also identified as an area that should have received greater attention in the Action Plan. This issue was included in Action Plan action 8, and actions carried out (see Section 4.2.2) included collaboration with the WHO, OIE, TATFAR, China and the Russian Federation and support for the implementation of national pharmaceutical policies⁶⁶ in 15 African countries in collaboration with the African, Caribbean and Pacific group of states (EC 2015c). However, an interviewee representing the WHO (INT24) stressed that the EC Action Plan was EU-focused and that the EU's activities on AMR would be strengthened by greater engagement beyond the EU, for example, by supporting the wider European region. Concrete action had been limited so far in this area, although discussions had taken place among EU and WHO/Europe representatives (INT24). In particular, there is overlap between member countries of the EU and WHO/Europe region, which means there could be some duplication of effort, such as requests to Member States in the context of monitoring and surveillance. The WHO published its European strategic Action Plan on antibiotic resistance (WHO/Europe 2011a) in 2011, the same year as the EC Action Plan, and the interviewee felt that this may have resulted in EU Member States being less engaged in the WHO's plan.

The Action Plan also needed a stronger international aid component: one interviewee indicated that there should have been more involvement from the Directorate-General for International Cooperation and Development (DG DEVCO) and EuropeAid (INT18), and another (INT13) suggested that South America in particular was one region that the EU had not addressed, and where the United States was doing more. Africa was also identified as a neglected region; lack of access to antimicrobials was perceived to be a bigger issue there than AMR (INT13; Årdal et al. 2016; Laxminarayan et al. 2016). Laxminarayan et al. (2016) report that limitations in access to antibiotics kill more people globally than does AMR, but that AMR remains a threat and that, as antibiotic consumption rises rapidly in humans and animals, it is important to promote responsible use of antibiotics.

A DG DEVCO representative (pers. comm. 2016) noted that existing EU health sector aid programmes focused on strengthening health systems. Commission representatives explained that the approach taken to mitigate the risk of AMR spreading through cross-border trade had been to focus on promoting AMR as an issue to be addressed internationally, as opposed to attempting to block European borders (INT2, INT3, INT7). One representative noted that resistance can also travel with people, and international AMR efforts would address its spread via food and people, but trade regulations would only be able to address its spread via food.

⁶⁶ Areas of focus included the quality assurance of medicines and the selection, prescribing and rational use of medicines.

5. EFFICIENCY — FINDINGS AND CONCLUSIONS

This section reports the findings and conclusions on the evaluation question related to the efficiency of the EC Action Plan.

5.1 Efficiency with which the EU budget was used to address the objectives of the Action Plan

Evaluation question 6: *Has the EU budget been efficiently used to address the objectives of the Action Plan?*

There were two main dimensions to address regarding the efficiency with which the EU budget was used to address the objectives of the Action Plan:

- Whether the EU budget allocated and spent for the Action Plan was consistent with Action Plan objectives; and
- Whether EU expenditure on the Action Plan was justified because it helped towards achieving objectives of the Action Plan and funding would not have been made available otherwise.

The findings on these core dimensions are discussed in this section.

R&D efforts require long time horizons to achieve results, and so it was too early to draw conclusions on the impact and outcomes of ongoing research and innovation activities.

5.1.1. Available data on EU spend on the Action Plan was focused on research

A review of EU documentation from 2011 to 2015 was undertaken to identify information on the scale of the EU budget aimed at addressing the objectives of the Action Plan and the allocation of that budget among activities. The documents reviewed included those published by ECDC and EFSA and organisations that fund research on AMR, including FP7, Horizon 2020 and the IMI. The AMR roadmap, AMR progress report (EC 2015c) and ECDC's annual reports of the director were particularly relevant. Where information was lacking, the study team contacted relevant experts for information and advice on accessing further budgetary information, including the ECDC, EMA (including ESAC, ESVAC and the Veterinary Medicines Department), EFSA, DG SANTE and the Directorate-General for Research and Innovation (DG RTD).

EU expenditure on Action Plan-related activities was diverse and involved a number of organisations. Spending on the Action Plan was generally not separately identified in financial reporting, although there were references to individual sums for particular purposes (Section 5.1.2).

The important exception was EU research spending attributed to AMR-related activity which was available by individual project. Research expenditures were made under three main EU programmes: FP7 (2007-2013); Horizon 2020 (2014-2020); and the IMI.

AMR research expenditure under the Seventh Programme for Research and Technological Development was €1.08 billion during the evaluation period. This funding included AMR research in a broad sense, including all funding for infectious diseases where treatment was affected by resistance (DG RTD correspondence, 10 December 2015; DG SANTE correspondence, 19 January 2015). Horizon 2020 also included in its first two years of operation (2014-2015) a set of new projects related to antibiotics. The EU Cordis website⁶⁷ identified a total of 76 Horizon 2020 projects that

⁶⁷ Cordis (2016a).

contained some reference to 'antibiotic' or 'antimicrobial' (48 refer to 'antibiotic', 15 to 'antimicrobial' and 13 to both). DG RTD estimated that €316 million was spent under Horizon 2020 through to the end of 2015 on AMR research in a broad sense, including all funding for infectious diseases where treatment is affected by resistance.

The IMI explicitly aims to establish collaborative projects with industry, including both large and small enterprises, and with universities, patient groups and regulators to improve the drug development process. A major focus of the IMI is to address the weakness of the pipeline for new antimicrobials under the Action Plan, particularly through the ND4BB programme (see Section 4.1.3.1). The EU committed €314 million to AMR research via the IMI (2013-2015). Through the IMI arrangement a further €382 million of resources was provided by the pharmaceutical industry, much of it in kind (e.g. access to laboratories, expert staff, equipment and other specialised resources). Overall, 11 pharmaceutical company members of EFPIA and 17 SMEs contributed alongside the EU. Total IMI resourcing for AMR-related research was nearly €700 million as a result of this combined effort. The IMI represents the largest multinational AMR R&D funding initiative in the world as of 2015 (Årdal et al. 2016).

Table 10: EU and industry funding of IMI ND4BB research projects, as at December 2015

ND4BB project	EU contribution (€)	Other funding (€)	Total funding (€)
TRANSLOCATION	15 984 202	13 343 803	29 328 005
COMBACTE	109 433 010	141 043 858	250 476 868
ENABLE	58 900 000	41 985 487	100 885 487
DRIVE-AB	6 299 987	4 534 477	10 834 464
COMBACTE-MAGNET	75 340 000	93 459 580	168 799 580
COMBACTE-CARE	23 871 500	61 648 301	85 519 801
iABC	24 331 609	26 353 521	50 685 130
Total	314 160 308	382 369 027	696 529 335

Source: <http://www.imi.europa.eu/content/nd4bb#TRANSLOCATION>

The majority of published, peer-reviewed, empirical analysis indicates that public and private funding of medical research complemented each other rather than substituting for one another.⁶⁸ Given the weakness of the antimicrobials pipeline, and that it is a requirement of IMI-funded projects to have private in-kind contributions, complementarity was assumed to apply to the IMI programme. Hence, the €700 million of antimicrobials R&D within the IMI was assumed to be additional to what would otherwise have occurred without the EU contribution.

Medical research takes many years, sometimes decades, to reach the point of producing new medicines or other treatments or preventive measures (Hanney et al. 2015), and although there was promise, few new antimicrobial treatments were developed during the evaluation period. Therefore, while the EU's research funding was allocated to an area of high priority, it was too early to determine whether it had led to the production of successful new treatments.

It is challenging to determine how much research funding should be devoted to a specific area and how much of that funding should come from EU programmes; however, two recent analyses have concluded that, overall, there is a need for greater investment in research to tackle AMR. An in-depth analysis carried out as part of a UK government review on AMR and published in 2015 by the O'Neill Review (2015b) said that AMR, as a global health threat, 'should arguably receive the same kind of public

⁶⁸ HERG et al. (2008) includes a review and summary of the relevant literature.

focus HIV/AIDS received in the 1990s or cancer research receives today — although it may not need the same levels of public funding to find a solution’ (O’Neill Review 2015b, 4). The O’Neill Review looked at the proportion of public health research spending devoted to AMR in Europe and the United States. While the authors were unable to obtain data to calculate these figures for all such spending across Europe, they concluded that spending proportions in Europe were likely similar to those in the United States, where AMR research received less than 2 % of the research funding allocated by the National Institutes of Health over the five years preceding publication of the report, while cancer research received 18.6 % (O’Neill Review 2015c).

The JPIAMR and the Commission recently supported a systematic analysis of antibacterial research funding across the 19 JPIAMR countries and at EU level over the period 2007-2013, categorising the projects funded according to the JPIAMR’s six priority areas (Kelly et al. 2015).⁶⁹ This assessment also concluded that AMR ‘clearly warrants increased and new investment from a range of sources’ (Kelly et al. 2015, 439), calling also for collaboration and coordination among funders. The JPIAMR study found a similar pattern in the proportion of research spending being devoted to AMR when looking at the UK (one of the biggest investors in AMR research among the JPIAMR members), where AMR research accounted for about 1 % of UK research councils’ spending during the period studied (Kelly et al. 2015).

The O’Neill Review indicated that while large-scale efforts to address AIDS, TB and malaria have made a big difference in stimulating drug development for those diseases, the push to address antibiotic development⁷⁰ has ‘barely started’ (O’Neill Review 2015b, 4). The review called for a global innovation fund for AMR and noted that the United States’ National Institutes of Health and the European Commission are two of the most significant sources of public research funding, which it described as the ‘lifeblood of early-stage activities’ in AMR-related research (O’Neill Review 2015b, 25).

The JPIAMR study found that EU funding accounts for a much higher percentage of AMR research funding than it does for research funding overall in the EU and European Free Trade Association countries (EU funding accounts for about 33 % of research funding for AMR, versus 7.5 % of research funding overall),⁷¹ which the authors took as a sign that national funding sources have not prioritised funding for AMR as much as has occurred at EU level or as much as the AMR threat warrants (Kelly et al. 2015). This finding, together with the conclusion that overall support for AMR research remains insufficient, strongly suggests that the support for AMR research that is being provided through EU programmes would not have been provided otherwise.

The authors of the JPIAMR review also assessed which AMR topics were receiving funding support, emphasising the importance of supporting the range of priorities relevant for AMR (Kelly et al. 2015). They found that European spending on AMR research was strongly weighted towards therapeutics.⁷² Among non-IMI EU-level

⁶⁹ The six priority areas are: therapeutics, diagnostics, surveillance, transmission, environment and interventions.

⁷⁰ Involving about US\$650 million in spending over five years through the ND4BB programme and the US Biomedical Advanced Research and Development Agency broad-spectrum antimicrobials programme.

⁷¹ The JPIAMR review found that €1.3 billion was spent in the period 2007-2013 in total by all sources studied, of which about half came from JPIAMR countries (€650 million) and half from EU sources (€660 million). Of the latter, €350 million supported the IMI and €310 million supported other EU programmes (Kelly et al. 2015).

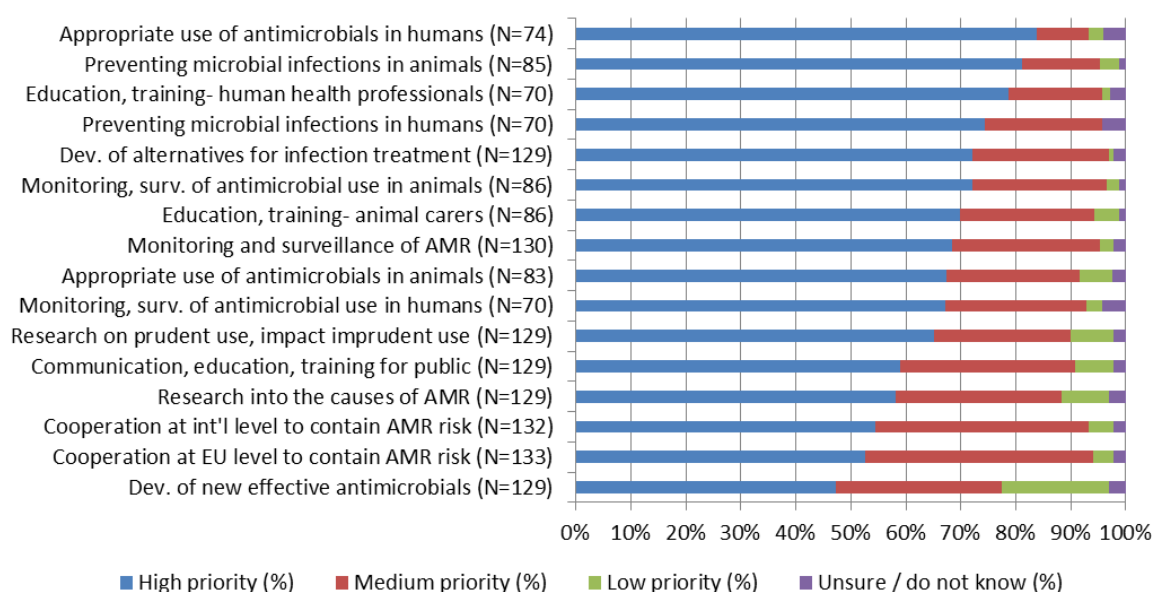
⁷² The JPIAMR’s Strategic Research Agenda describes the therapeutics priority topic as ‘Development of novel antibiotics and alternatives for antibiotics — from basic research to the market’ (JPIAMR 2013b, 9).

programmes, 63 % of funding was spent on projects related to therapeutics, while 13 % was spent on transmission, 12 % on diagnostics, 7 % on interventions, 3 % on surveillance and 2 % on environment. Among the nine IMI projects reviewed, most relate to therapeutics, while also supporting the development of European research infrastructure (Kelly et al. 2015). At the national level, there was a similar pattern: 66 % of funding supported projects related to therapeutics. While it was not clear what distribution of support across topics would be ideal, the observed distribution broadly reflects the objectives of the Action Plan, which includes two actions focused specifically on the development of new antibiotics (actions 6 and 7) and one action covering all other aspects of AMR research (action 11).⁷³

The targeted surveys conducted for this evaluation asked about the relative priorities that should be attached to different areas of EU spending on actions against AMR (Figure 10). For topics related to R&D, responses to this question were consistent with findings from both stakeholder workshops and interviews, which identified the need to widen the scope of R&D beyond traditional antibiotics (see Section 4.1.3.3). The development of new, effective antimicrobials ranked lowest in priority among all areas (not only research-related issues): only 47 % of respondents judged it 'high priority', compared with the development of alternatives for treatment of microbial infections, which was considered a high priority by 72 % of respondents. Research into new antimicrobials also received the highest proportion of responses, indicating that this is a 'low priority' area (19 %, compared with 9 % on research into causes of AMR, the area with the second largest proportion of 'low priority' responses). The perception that a large proportion of EU research funding has been invested in research related to the development of antimicrobials was supported by the evidence that spending was weighted towards therapeutics.

⁷³ Though these data do not fully reflect the 2011-2015 period, they overlap with that period and represent the most recent information available.

Figure 10: Member State representatives' and stakeholders' priorities for EU financial support



Source: Stakeholder and Member State surveys (conducted in 2015).

Note: Activity areas are ordered from high to low by percentage of respondents ranking each as a high priority. Abbreviations used: Dev.= Development; surv.= surveillance; int'l= international.

The other R&D topics covered in the survey were (i) research on prudent use of antimicrobials and the impacts of imprudent use, which was ranked a high priority by 65 % of respondents and a low priority by 8 %, and (ii) research into the causes of AMR, which was ranked a high priority by 58 % of respondents and a low priority by 9 %.

5.1.2. Information on non-research areas of EU spend was limited

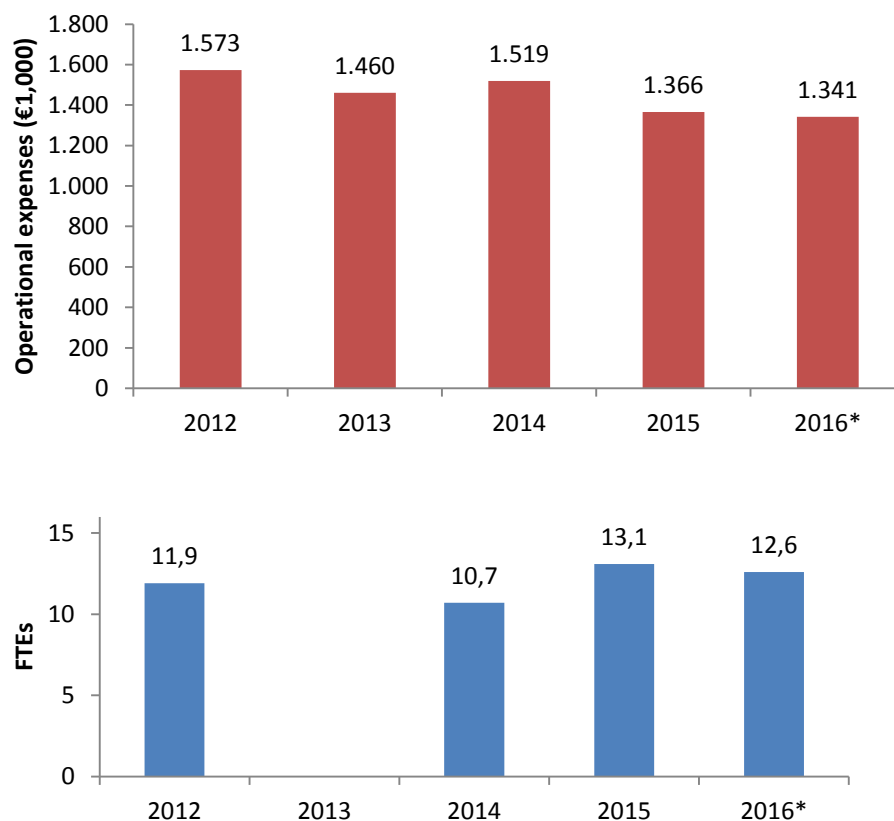
Other EU expenditures in support of the Action Plan that were identified were much smaller than the sums committed by the EU to AMR-related research. A €2 million European Commission Coordination and Support Action grant⁷⁴ was awarded through FP7 in 2012 to the JPIAMR (Cordis 2016b). A review of ECDC annual reports revealed that spending on the Antimicrobial Resistance and Healthcare-associated Infections (ARHAI) programme, which focuses on surveillance, scientific advice, training and communication related to AMR and HAIs, totalled approximately €2.7 million in 2014 (ECDC 2015g), which was equivalent to 4.4 % of total ECDC expenditure in that year. Other publically available documents from the ECDC management board revealed further details of spending on ARHAI (these estimates were not directly comparable to the figures in the ECDC annual report). In 2016, for example, the total budget for ARHAI was approximately €3.3 million (equivalent to 5.6 % of total ECDC expenditure in that year), of which €1.3 million was described as operational expenses.

Further detail on full time equivalent (FTE) employees and operational expenses were also available for all years of the Action Plan (Figure 11). These showed that the budget for operational expenses fell by about 15 % from 2012 and that the number of FTEs increased slightly in recent years (from 11.9 in 2012, to 13.1 in 2015, to 12.6 in 2016). Correspondence with ECDC indicated that these figures did not include AMR-related activities implemented by other disease programmes at ECDC (e.g. tuberculosis or sexually transmitted diseases) and that it was not possible to ascertain which fraction of those budgets was AMR-related (although it was estimated that it

⁷⁴ Project reference number 323209.

would represent an increase of about 10 % in the reported resources allocated to AMR). Furthermore, it was not possible to know which of this funding was directly related to the AMR Action Plan.

Figure 11: Operational expenses budget (top) and FTEs (bottom) for the ECDC's Antimicrobial Resistance and Healthcare-associated Infections programme (2012-2016)



Source: ECDC.

Notes:

1. Operational expenses excluded staff and administrative expenses (data were not available from ECDC).
2. Of the 2016 operational expenses figure, €7.6 million was for surveillance, €377 000 for scientific advice, €80 000 for public health training and €120 000 for health communication.
3. FTE data were not reported for 2013.
4. Of the 2016 FTEs figure, 4.4 were for surveillance and epidemic intelligence work, 7.2 for scientific support, 0.2 for training and capacity building and 0.8 for communication.

* 2016 figures represent anticipated spending.

EFSA had significant annual spend in relation to AMR but was unable to provide information on resources spent specifically on AMR (EFSA pers. comm. 2015). Other EU bodies made expenditures in areas related to the Action Plan, such as the EMA funding ESVAC and the Commission co-financing the costs incurred by Member States when carrying out compulsory AMR monitoring in the context of veterinary medicine (EC 2015c), but in most cases details on these expenditures were not published and could not be obtained.⁷⁵

⁷⁵ DG SANTE Unit D6 (Medicinal Products — Quality, Safety and Efficacy) provided information, including the fact that €17 500 was spent on activities related to AMR during the period 2011-2015. This includes expenses related to a 2012 meeting on the revision of the veterinary medicines legislation (€2 886),

The targeted survey for this evaluation asked whether respondents were aware of any ways in which the allocation of EU spending on AMR was inappropriate or inefficient. This question was answered by 134 stakeholders and Member State officials: 103 (77 %) said they were not aware of inappropriate or inefficient allocation of EU spending, but 31 (23 %) said, 'yes', they were aware of that kind of problem. No consistent themes emerged from the examples of inefficiencies or inappropriateness that were given, although some respondents referred to a lack of specific and concrete steps to improve disease diagnostics in humans and animals. Two respondents claimed that too much emphasis had been placed on restricting use of antimicrobials in the veterinary/farming sector. One respondent identified a lack of investment specifically in diagnostics for animals, noting as reasons for this the commercial unattractiveness of diagnostics, the existence of 'regulatory barriers (some methods are accepted and others are not, no harmonisation of regulatory acceptance, or restriction to some labs only)', and the possibility that established diagnostic laboratories may have resisted the spread of pen-side diagnostic tests.

The limited evidence available therefore suggested that the areas outside research where spending occurred (i.e. monitoring and surveillance, and communication, education and training) were consistent with Action Plan objectives and that resources were efficiently used. However, the lack of published budget or expenditure data at the level of disaggregation necessary to identify AMR-related activities meant that conclusions about the efficiency of EU expenditure could not be readily drawn. Several of the EU agencies contacted indicated that it would be highly desirable to develop better accounting systems so that AMR-related resources could be properly reported on and monitored.

a 2015 workshop on the impact on public health and animal health of the use of antibiotics in animals (€13 118), and travel (a conference in Copenhagen in 2012 'Combatting AMR — Time for Joint Action', an EMA stakeholders meeting on antimicrobials in London in 2014, an OECD workshop on AMR in Paris in 2015, and a TATFAR meeting in Luxembourg in 2015 (€1 497).

6. COHERENCE — FINDINGS AND CONCLUSIONS

This section reports the findings and conclusions on evaluation questions related to the coherence of the EC Action Plan.

6.1 Coherence of the Action Plan with Member States' national or regional strategies and similar international-level initiatives

Evaluation question 7: *To what extent is the Action Plan coherent with Member States' national (or regional) strategies and action plans and with similar initiatives at the international level?*

This evaluation question addressed the extent to which the EC Action Plan was coherent with Member State action plans and with similar initiatives at the international level. The relevant judgement criteria relate to the complementarity of the EC Action Plan with other regional, national and international strategies and actions and to consistency of the objectives across strategies.

6.1.1. The EC Action Plan generally complemented national and regional policies on AMR, and in some cases it directly influenced them

One indicator of the coherence of the EC Action Plan with national approaches was the extent to which it influenced national policies on AMR and aligned with plans in place prior to its implementation. Fourteen Member State AMR action plans or strategies were launched in 2014 or 2015 (Dumartin 2015),⁷⁶ and representatives from 14 Member States indicated in the survey that the development of their national policy was influenced by the EC Action Plan.⁷⁷ Thirteen countries released their first Action Plan prior to 2011 (the year the EC Action Plan was published) (Dumartin 2015); some of these action plans have been revised since 2011 and may also have been influenced by the EC Action Plan.

Respondents from four Member States stated that their national policy predated the EC Action Plan,⁷⁸ and respondents from four reported that their national policy was formulated independently of the EC Action Plan.⁷⁹ In some cases, there were respondents from the same Member State indicating that the Action Plan influenced their national policy and those indicating that their plan predated the EC Action Plan or was developed independently. This overlap may reflect variable levels of familiarity with the development of the national plans or the existence of multiple relevant policies/plans within a Member State. Overall, these results indicate that the Action Plan influenced AMR policies in at least half of the EU Member States. The next section assesses the extent to which the scope and content of national action plans cohered with the EC Action Plan, and *vice versa*.

6.1.1.1. The EC Action Plan and national action plans addressed similar issues

One indicator of the coherence of the EC Action Plan with national approaches was the scope of national policies compared with the EC Action Plan. The EC Action Plan had seven overarching objectives, which focused on prevention; surveillance; appropriate use of antibiotics; developing effective antimicrobials or alternatives for treatment;

⁷⁶ The reference does not identify the 14 Member States.

⁷⁷ 43 responses were received, covering 14 Member States: AT [3], BE, HR [2], DK, EE [2], HU [2], LV [2], LT, NL, PT, RO [2], SI, ES [2] and UK.

⁷⁸ AT, NL, SI [2] and SE [2].

⁷⁹ BE, DK, FI [2] and FR [3].

reinforcing research and innovation; monitoring and surveillance; and improved communication, education and training. Within these overarching objectives, the EC Action Plan contained specific actions relating to human health, animal health, international collaboration, coordinating research efforts and education.

Member State survey respondents were also asked to compare their national AMR policies with the EC Action Plan. Representatives of nine Member States (26 % of Member State survey respondents) reported that the EC Action Plan was broader in scope (i.e. some areas of the EC Action Plan were not addressed by the national policy).⁸⁰ Representatives of 16 Member States (61 % of Member State survey respondents) indicated that their national policy and the EC Action Plan had similar scope.⁸¹ Representatives from Sweden and the Netherlands responded that their national policy was broader in scope (i.e. some areas of the national policy were not addressed by the EC Action Plan).

The most notable comparison between the EC Action Plan and national-level action plans was the extent to which they addressed the 'one health' approach, which required an interdisciplinary and multi-stakeholder collaboration. Among the 20 European action plans or strategies in place, 18 were inter-sectoral, bringing together aspects of AMR and the prudent use of antimicrobials in veterinary medicine and/or the food chain alongside human health — an approach aligned with the EC Action Plan aim of capturing a holistic approach. The following sections provide evidence gathered on the coherence of the EC Action Plan with national policies in specific areas. Information was obtained primarily through the Member State survey (summarised in Table 11) and a review of a subset of Member State policy documents.⁸²

⁸⁰ Austria, Belgium [3], Croatia, Estonia, Finland [2], Hungary, Latvia [2], Lithuania and Slovenia.

⁸¹ Austria [3], Bulgaria, Croatia, Cyprus, Denmark [2], Estonia, France [3], Germany, Hungary, Italy, Portugal, Romania [2], Slovenia [2], Spain [2], Sweden and UK.

⁸² Documents from the following nine Member States were reviewed as part of the evaluation's desk research phase: Austria, Denmark, France, Germany, Ireland, the Netherlands, Portugal, Sweden and UK. They were selected on the basis of online accessibility and language.

Table 11: Summary of Member State survey responses regarding complementarity between the EC Action Plan and national policies/priorities related to AMR

To what extent do the objectives of the EC Action Plan complement the national policies/priorities related to AMR in your country?

Rank	AMR policy area	No. of responses	Percentage of total responses (no. of responses)	
			Partly or fully complements	Does not complement
1	Communication , education and training for people caring for animals	42	93% (39)	0% (0)
2	Monitoring and surveillance of antimicrobial use in animals	40	93% (37)	0% (0)
3	Monitoring and surveillance of AMR	61	92% (56)	0% (0)
4	Cooperation at EU level to contain the risk of antimicrobial resistance	59	88% (52)	3% (2)
5	Monitoring and surveillance of antimicrobial use in humans	26	88% (23)	0% (0)
6	Communication , education and training for human health professionals	26	88% (23)	0% (0)
7	Appropriate use of antimicrobials in humans	26	88% (23)	4% (1)
8	Communication , education and training for the general public	59	86% (51)	0% (0)
9	Appropriate use of antimicrobials in animals	41	85% (35)	2% (1)
10	Prevention of microbial infections and their spread in animals	40	85% (34)	3% (1)
11	Prevention of microbial infections and their spread in humans	25	84% (21)	4% (1)
12	Cooperation at international level to contain the risk of AMR	59	83% (49)	2% (1)
13	Research into the causes of antimicrobial resistance	59	75% (44)	5% (3)
14	Research into the prudent use of antimicrobials and impact of imprudent use	58	71% (41)	5% (3)
15	Development of alternatives for treatment of microbial infections	58	57% (33)	14% (8)
16	Development of new, effective antimicrobials	59	47% (28)	14% (8)

Note: Topics are ranked by the percentage in the fourth column and colour-coded by objective. Variability in the total number of responses reflects differences in the numbers of respondents self-identifying as having expertise in human versus animal health (or both). Percentages are

rounded to the nearest 1 %. Respondents could also mark 'unsure/do not know' or 'not applicable'.

Ensuring appropriate use of antimicrobials in animals and humans was an objective across AMR policies, and the EC Action Plan complemented national policies.

Ensuring antimicrobials were used appropriately and prudently was an objective across strategies and action plans, and the EC Action Plan was complementary to national policies in this area. The majority of Member State survey respondents indicated that the EC Action Plan objectives in this area fully or at least partly complemented their national policies in both animal health (85 % of respondents) and human health (88 % of respondents) (Table 11). Member States' AMR policies also influenced EU policies in this area prior to the introduction of the Action Plan. For example, Denmark and Sweden have action plans that predated the EC Action Plan which include bans on using antibiotics as growth promoters in animals, and this influenced the EU's decision to make a similar EU-wide ruling in 2006 (INT2, INT3).

Developing new, effective antimicrobials or alternatives and reinforcing research and innovation were complementary objectives between the EC Action Plan and national strategies.

The EC Action Plan included two objectives related to research and innovation, one focused on treatment development and one on other aspects of research and research coordination, such as promoting research on pathogen-host interactions and supporting an initiative to coordinate national AMR research activities.

Some Member States have objectives similar to the EU objective of developing new, effective antimicrobials or alternatives to treatment. For example, the Netherlands' strategy targets product innovation and innovation to prevent and control infections, as well as developing alternatives to antibiotics (Ministry of Health, Welfare and Sport 2015), and the UK promotes the development of new medicinal products and vaccinations. In animal health, France's and Portugal's action plans focus on developing alternatives to antibiotics (France) and the evaluation of alternative treatments (Portugal). Seventeen EU Member States participate in the JPIAMR, adding a significant contribution to complement EU support for AMR-related research (see Section 5.1.1) (EC 2015c).

Cooperation with partners to contain the risks of AMR was complementary to national policies.

The survey responses indicated that the EC Action Plan generally complemented national policies on cooperation with international partners — 88 % of respondents (52 out of 59) indicated that the EC Action Plan either fully or partly complemented objectives on cooperation within the EU to contain the risk of AMR, and only two respondents stated that the EU action did not complement national cooperation priorities or policies. Regarding cooperation at international level, 83 % of respondents stated that the EC Action Plan either fully or partly complemented national policies and priorities.

Improving monitoring and surveillance in animal and human medicine were complementary objectives between the EU and Member State AMR policies.

Member State policies also included objectives on monitoring and surveillance. Similar to the EC Action Plan, they broadly referred to the importance of gathering data for surveillance of AMR and antimicrobial consumption, and they focused on strengthening surveillance efforts. There was strong complementarity between Member State and EU policies in this area, with most survey respondents reporting that there was at least partial complementarity in monitoring and surveillance of antimicrobial use in animals

(93 % of respondents, 37 out of 40), AMR (92 % of respondents, 56 out of 61), and antimicrobial use in humans (88 % of respondents, 23 out of 26).

Improving communication, education and training were highly complementary between the EC Action Plan and national policies.

Most national AMR action plans and strategies sought to improve awareness, education and training on AMR among the general public and health professionals. Complementarity of these policies with the EC Action Plan was also high in this area. Across communication, education and training for each of animal health professionals, human health professionals and the general public, the EC Action Plan was identified as at least partly complementary to national policies by at least 86 % of respondents.

Related to its objective of improving communication, education and training, the Action Plan referred to the importance of education campaigns, such as European Antibiotics Awareness Day, and it set out in action 12 to assess public awareness of AMR and the appropriate use of antimicrobials. According to a recent Commission survey of 29 European countries (Dumartin 2015), 24 countries carried out awareness-raising campaigns for the general public (compared with 17 in 2008) – activities coherent with this objective and related to action 12. In addition, coherent with the Action Plan's action 4 (on strengthening infection prevention and control in healthcare settings), most countries (90 %) covered topics related to AMR and prudent use of antimicrobials in the curriculum for training doctors and pharmacists (Dumartin 2015). Smaller percentages of the countries surveyed covered AMR topics in training for nurses (17 % cover AMR), dentists and midwives (14 % cover AMR), and veterinarians (34 % cover AMR) (Dumartin 2015).

Case studies 3 and 6, which focused on education and awareness programmes in the UK and France, respectively (Appendix N), explored how these Member States were working to achieve their aims in this area and links to EU action. The French case study found that a major French public health campaign predating the Action Plan helped encourage the establishment in 2008 of EAAD, an awareness initiative mentioned in the Action Plan. The UK case study was linked to EU-level initiatives by making use of European e-Bug resources and professional networking (one of its creators was an individual who engaged with EU policymakers in this area).

6.1.1.2. The EC Action Plan could have been more coherent if the breadth of its coverage of environmental issues had encompassed a wider range of issues

Generally, the seven overarching objectives of the EC Action Plan were consistent with those in national action plans and strategies. However, the EC Action Plan addressed the environmental context to a limited extent under action 8. EU environment policy aims to help protect nature, safeguard the health and wellbeing of people in the EU and promote green growth and sustainable development. While the Action Plan was not inconsistent with EU policy on the environment, it could have been more coherent if the breadth of its coverage of environmental issues had encompassed a wider range of issues, including the impacts of agricultural and human waste on AMR transmission.

This does not align with some other national action plans (e.g. France, Germany, the Netherlands, Sweden and the UK), which include a more overarching environmental objective and/or focus on other aspects of the environment.

Member States took different approaches to addressing the environment in their AMR policies. The French Action Plan, in considering how to preserve the effectiveness of antibiotics, states that environmental concerns needed be taken into account in the veterinary context (Ministère du travail, de l'emploi et de la santé 2011). The UK addressed the potential role of the environment in the transmission of AMR with a plan to integrate 'human veterinary and environmental surveillance data to improve [...] understanding of the epidemiology' (Department of Health 2013). The UK also sought

to understand the impact that the built environment had on infection control (Department of Health 2013). Sweden identified a need to map the impacts of antibiotic use on the environment, particularly through the use of genes that are markers of antibiotic resistance intended for use in the human or veterinary contexts. Germany's Action Plan called for more work in terms of understanding resistant pathogens (Federal Ministry of Health 2015), while the Netherlands took a more general approach by including antibiotic-resistance issues in national action plans and initiatives for other areas (especially in wastewater) (Ministry of Health, Welfare and Sport 2015).

6.1.1.3. The EC Action Plan was coherent with other international-level initiatives

International bodies also implemented strategies or action plans on AMR, and 92 % of Member State representatives who responded to the survey indicated that the activities of these international organisations were well coordinated with Member States in the EU.⁸³ Primary among these strategies and action plans were the WHO's European and global action plans. The 2015 WHO global Action Plan included five overarching objectives (WHO 2015a):

1. Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.
2. Strengthen the knowledge and evidence base through surveillance and research.
3. Reduce the incidence of infection through effective sanitation, hygiene and infection-prevention measures.
4. Optimize the use of antimicrobial medicines in human and animal health.
5. Develop the economic case for sustainable investment that takes account of the needs of all countries and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

These objectives generally match the seven objectives of the EC Action Plan, indicating broad coherence between the two plans. One difference is that the EC Action Plan does not include an objective that is completely analogous to the WHO's fifth objective of ensuring sustainable investment in addressing AMR. This broad objective covers investment across areas, including country needs for tackling AMR (particularly in developing countries, an area that was not emphasised in the EC Action Plan), and areas that are consistent with the EC Action Plan: basic scientific research, strengthening of public-private partnerships to encourage R&D in the development of antimicrobials and diagnostics, and related innovation. Consistent with the EC Action Plan, the objective also covers collaboration with the FAO and OIE to address AMR, with a focus on animal health and agriculture; collaboration and coordination across countries, private organisations and others; and the adoption of new market models to encourage innovation in antimicrobials and ensure access to treatments (WHO 2015a). The WHO plan calls for increased investment in diagnostics, vaccines, medicines and other interventions (WHO 2015a), which is coherent with the EU's research and development objectives, although the EC Action Plan places less emphasis on R&D related to diagnostics and vaccines compared with R&D related to antibiotics and alternatives to the treatment of infections.

Another difference between the EU's plan and WHO global Action Plan is that the WHO explicitly encourages Member States to put in place their own national action plans

⁸³ Respondents were asked about activities relating to the WHO, OIE, FAO and TATFAR.

within two years of the WHO global Action Plan's endorsement by the World Health Assembly (WHO 2015a). No similar objective was explicitly included in the EC Action Plan, although as explained in EQ1, the Commission's Guidelines for the prudent use of antimicrobials in veterinary medicine called on Member States to develop a holistic strategy and/or Action Plan to address AMR.

Like the WHO global Action Plan, the WHO/Europe Action Plan⁸⁴ shares overarching goals with the EC Action Plan (WHO/Europe 2011a). The WHO/Europe Action Plan, also published in 2011, set out seven objectives which were broadly consistent with the EC Action Plan's objectives (see EQ1). The EC Action Plan also set out to capture a holistic, or 'one health', approach — an aim aligned with the first of the WHO/Europe Action Plan's objectives.

TATFAR, established in 2009, with the EU and United States as its founding members, aims to help build understanding between members' governments about their AMR initiatives and to promote information exchange and collaboration. TATFAR was renewed and extended twice: in 2013 (to 2015), with collaboration efforts extended to include Canada and Norway (EC 2015c), and again in 2015 (2016-2020).⁸⁵ TATFAR established three focus areas (see EQ4) and, subsequent to its 2014 progress report (TATFAR 2014), worked on 16 recommendations related to these areas. Overall, the Action Plan was coherent with TATFAR activities (INT23).

The three focus areas of TATFAR were (TATFAR 2014):

- Appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities;
- Prevention of both healthcare- and community-associated drug-resistant infections; and
- Strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between the members.

The specific recommendations under these areas mainly focused on collaboration, communication and information sharing across the EU and the United States and complemented EC Action Plan objectives relating to the development of new antimicrobials, infection prevention and appropriate use, as well as strengthening of bilateral commitments.

TATFAR also provided a venue for cooperation that could lead to enhanced coherence between EU and United States policies on AMR. An interviewee representing a European agency and who was involved with TATFAR (INT23) suggested that one area where the EU and United States could work together was to develop approaches for measuring antimicrobial sales per animal species, an issue facing both. In addition, TATFAR was cited in both the EC Action Plan and the United States national Action Plan (White House 2015), suggesting that coherence between the EC Action Plan and TATFAR was explicitly considered when the EC Action Plan was developed. Individuals active in dealing with AMR in the EU were also involved with TATFAR, enabling recommendations and actions to be developed in a coherent way; one interviewee involved with TATFAR stressed that there was a high level of coherence between the EC Action Plan and TATFAR because TATFAR was mainly about coordination (INT23).

6.2 Coherence of the Action Plan with other EU policies

⁸⁴ The WHO European region covers 53 countries.

⁸⁵ CDC (2015).

Evaluation question 8: *To what extent are the actions contained in the Action Plan coherent with other EU policies on the environment, human health, animal health and welfare, food safety, agriculture, research, competitiveness and SMEs?*

This evaluation question addressed the extent to which the actions contained in the EC Action Plan were coherent with other EU policies on the environment, human health, animal health and welfare, food safety, agriculture, research, competitiveness and SMEs. The judgement criteria for this question assessed whether or not the actions of the EC Action Plan on AMR were coherent with those set out in other relevant EU policies.

6.2.1. The Action Plan was coherent with other EU policies

The Action Plan linked to and built on existing policy initiatives in several areas, in particular human health, animal health and welfare, research, competitiveness and SMEs. It brought progress towards the introduction of new policies related to animal health and food safety. Overall, the EC Action Plan was coherent with other EU policies.

6.2.1.1. The Action Plan was coherent with EU policy on human health

EU health policy aims to complement national policies in ensuring that all of the people in the EU have access to quality healthcare by protecting people from health threats that affect more than one EU Member State, preventing disease, improving access to healthcare, promoting health education, and improving patient safety (EC 2016b). The EU also has a role in introducing EU-wide standards and regulations to ensure the quality of medicinal products and medical devices, supporting Member States in cooperation and the identification of best practices, and funding public health projects (EU 2016a).

The Action Plan drew directly on existing EU recommendations in health policy. Under action 1, on strengthening the promotion of the appropriate use of antimicrobials in all Member States, the Action Plan sought to ensure effective implementation by Member States of the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicines. Action 4, on strengthening infection prevention and control in health settings, focused on assessing and reporting on progress made by the Member States in implementing the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections. Action 9, on strengthening surveillance on AMR and antimicrobial consumption in human medicine, and action 12, on monitoring public awareness about AMR, are consistent with EU human health policy because they support the collection of relevant evidence that can inform EU and national health policies. In the survey, 78 % of respondents agreed or strongly agreed that EU AMR policy complements and/or reinforces EU policy on human health, while 2 % disagreed and 20 % were unsure.

6.2.1.2. The Action Plan was coherent with EU policy on animal health and welfare and on food safety

EU policy on animal health and welfare aims to safeguard human and animal health and welfare in addition to protecting food safety. It works to control disease outbreaks, run surveillance and eradication programmes and ensure the safety of the EU internal market while permitting trade. EU food safety policy aims to assure animal health and welfare in addition to food safety and plant health through the implementation of controls, management of international relations, collaboration with EFSA and the use of science-based risk management (EC 2016a).

The Action Plan was coherent with EU policy in these areas. Under action 5, the Action Plan called for the introduction of a new Animal Health Law. In line with animal health policy objectives, the law was consolidated and existing rules amended, aiming to

prevent and control infections, raise awareness of disease, reduce the use of antibiotics, and improve the traceability of animals. Action 3 focused on introducing recommendations for prudent use in veterinary medicine to manage risks to human and animal health that arise from the use of antimicrobials in veterinary medicine. The Commission adopted proposals to revise legislation on veterinary medicinal products and medicated feed. Action 10, on strengthening surveillance systems on the consumption of antimicrobials for use in animals and AMR in zoonotic and indicator (commensal) bacteria, helped to improve the evidence base for risk management. The sub-action (under action 8) to further develop the OIE health codes and promote implementation of international Codex Alimentarius standards was in line with the aims of EU policy in animal health and food safety.

In the survey, 80 % of respondents agreed or strongly agreed that EU AMR policy complements and/or reinforces EU policy on animal health and welfare, while 8 % disagreed and 12 % were unsure. For food safety, 75 % of respondents agreed or strongly agreed that EU policies on AMR were complementary, while 7 % disagreed or strongly disagreed and 18 % were unsure.

6.2.1.3. The Action Plan was coherent with EU policy on agriculture

EU agricultural policy, which centres on the common agricultural policy, focuses on ensuring that food production is safe, diverse and environmentally sustainable; creating jobs; and supporting innovation and its uptake in the European food sector. Through its links to animal health and welfare and food safety, the EC Action Plan is consistent with EU agricultural policy. Common agricultural policy objectives enabled action related to AMR, such as improvement of on-farm hygiene. However, it is up to the Member States to choose which of the relevant measures they want to include in their rural development programmes (INT2, INT3). In the survey, 59 % of respondents agreed or strongly agreed that EU AMR policy complements and/or reinforces EU agricultural policy, while 11 % disagreed or strongly disagreed and 30 % were unsure.

6.2.1.4. The Action Plan was coherent with EU policy on research, competitiveness and SMEs

EU policy on research is designed to develop and implement research and innovation policy in Europe to support EU competitiveness, boost growth, create jobs, and tackle societal challenges (DG RTD 2016).⁸⁶ The EU aims to support competitiveness through a set of policy mechanisms, including country-specific recommendations designed to highlight structural issues, innovation policy initiatives such as Horizon 2020, and measures to nurture SMEs (DG Growth 2016a). EU SME policy, centred on the Small Business Act for Europe (COM/2008/0394), aims to encourage entrepreneurship, simplify the regulatory and policy environment for SMEs, increase internationalisation and access to new markets and facilitate access to finance (DG Growth 2016b).

The Action Plan supported the aims of EU competitiveness and SME policy by supporting innovative SMEs active in areas related to AMR. It was coherent with EU policy in these areas, and it built on existing research and innovation support mechanisms. Under action 11, on reinforcing and coordinating research efforts, the Action Plan set out to promote research in different aspects of AMR. This support has come largely through the EU's research and innovation programmes FP7 (2007-2013) and Horizon 2020 (2014-2020). Supporting innovative SMEs was an objective of both programmes. Horizon 2020 includes a dedicated SME funding instrument, and 44 innovative SMEs were directly supported through funding for AMR-related projects

⁸⁶ Two of the societal challenges identified as important funding priorities for the Horizon 2020 programme are particularly relevant for AMR: (i) health, demographic change and wellbeing and (ii) food security, sustainable agriculture and forestry, marine and maritime and inland water research, and the bioeconomy.

under FP7 (EC 2015c). In addition, the European Commission facilitated the establishment of the BEAM Alliance in 2015 (BEAM Alliance 2015), a platform bringing together small European companies active in innovation to tackle AMR (DG RTD pers. comm. 2015).

Under action 7, on promoting efforts to analyse the need for new antibiotics in veterinary medicine, activities were carried out to clarify the need for veterinary antimicrobials and, potentially, the need for incentives to stimulate their development. The introduction of such incentives could stimulate innovation in this area, in line with EU policy objectives related to SMEs and competitiveness. The proposal on veterinary medicinal products developed under action 2 may help address this issue, for example, through an extended data protection period for new veterinary antimicrobials. As discussed elsewhere, however, a lack of incentives for developing new veterinary antimicrobials remains a major challenge.

Under action 6, on promoting collaborative R&D efforts to bring new antibiotics to patients, the Action Plan launched the major public-private partnership programme ND4BB within the framework of the IMI. Consistent with EU policy objectives related to competitiveness and SMEs, the IMI encourages innovation by facilitating collaboration among universities, the pharmaceutical industry and other industry, SMEs, regulators and patient organisations (IMI 2016).

In the survey, 77 % of respondents agreed or strongly agreed that EU AMR policy complements and/or reinforces EU research policy, while 20 % were unsure. For competitiveness policy, 40 % agreed or strongly agreed that AMR policy was complementary (45 % were unsure). For SMEs, just 27 % agreed or strongly agreed that AMR policy complemented or reinforced existing EU policies, while 62 % were unsure.

6.2.1.5. The Action Plan was consistent with EU policy on the environment, but its coverage of environmental issues was limited

EU environmental policy aims to help protect nature, safeguard the health and wellbeing of people in the EU, promote green growth of the EU economy and promote sustainable development globally (EU 2016b). The safeguarding of health and wellbeing is of particular relevance for AMR, which includes reducing or eliminating the effects of harmful chemicals. Action 8 addressed environmental pollution from antimicrobial medicines, and this activity is consistent with EU environmental policy, but it did not extend to other issues that fall under the EU environmental policy remit. In the survey, 56 % of respondents agreed or strongly agreed that EU AMR policy complements and/or reinforces EU environmental policy, while 14 % disagreed or strongly disagreed and 30 % were unsure.

7. EU ADDED VALUE — FINDINGS AND CONCLUSIONS

This section reports the findings and conclusions on evaluation questions related to the added value of the EC Action Plan.

7.1 Assessment of added value resulting from the EC Action Plan

Evaluation question 9: *What is the added value resulting from the EC Action Plan compared with what could be achieved by Member States at national and/or regional levels? Did the EC Action Plan identify the actions which should be best dealt with at EU level?*

This evaluation question identified the contribution of the Action Plan relative to what would have been achieved in its absence and assessed whether it focused on appropriate actions to address at EU level. The judgement criteria cover whether the Action Plan led to results beyond what could have been achieved by Member State or regional actions alone and whether the Action Plan identified actions best dealt with at EU level. The related evaluation indicators assessed evidence that discontinuation of actions under the Action Plan may have had negative consequences for the situation on AMR in the EU and whether improvements could be viewed as a result of Member State efforts and initiatives alone. Indicators also assessed evidence of a detrimental impact on existing Member State actions for tackling AMR (or lack thereof), the existence of a clear link between the characteristics of the AMR challenge and the need for action at the EU level and whether areas for EU action were appropriate in view of EU and national competencies (as assessed in EQ2).

7.1.1. The Action Plan helped build political momentum on AMR

The Action Plan demonstrated political commitment, gave direction to the agencies and DGs tasked with carrying out specific actions at EU level and ensured that financing related to AMR activities remained a priority (INT7, INT18, INT23). A representative of DG SANTE explained that the Action Plan created political momentum that helped drive EU implementation of activities to address AMR and build awareness and encourage activity at the international level because it was supported by the Council of the EU and the European Parliament (INT7).

A majority of survey respondents (84 %, 114 out of 135) stated that they 'agreed' or 'strongly agreed' that the Action Plan identified actions best dealt with at EU level. Only six respondents (4 %) disagreed. No respondents responded 'strongly disagree'. The level of agreement was similar across respondents whose stated expertise was in animal health, human health or both. One respondent commented in the survey that AMR 'is a global problem. Accordingly, it can only be solved by global actors. As we do not have such, we must at least solve it regionally in [the] EU'.

Interviewees and workshop participants indicated that the Action Plan also helped raise awareness on a global level and set an example for other parts of the world. Participants in the first stakeholder workshop observed that the Action Plan played an important role in enabling and promoting coordination at both the EU and global levels, and they identified this role as its main contribution to tackling AMR. An EU agency representative remarked that Europe was seen globally as setting the best example for control and use of antimicrobials (INT23). A DG SANTE representative (INT12) and an independent expert (INT15) also stressed the symbolic value of having an EU-level Action Plan in the specific priority areas. An independent expert (INT18) likened AMR to climate change, noting that both issues required global discussions and strong leadership and that both came with collective responsibility. Furthermore, AMR travels across borders and so must be addressed on a regional and an international scale (INT18, INT23). An interviewee from DG SANTE cited growing interest from third countries in having EU-supported conferences and workshops about how to tackle AMR

and noted that the EU's monitoring programmes and work harmonising human and animal data attracted particular interest (INT7).

Changes in antimicrobial resistance and consumption patterns could not be linked to the Action Plan, however, because it was too early at the time of the evaluation to attribute changes observed to the Action Plan and because any observed effects could not be disentangled from other activities aimed to address AMR in the EU and beyond.

7.1.2. The Action Plan played an important role in coordinating, prioritising and harmonising EU activities and policies at national level

Overall, evidence gathered through the surveys, interviews and workshop indicated that the EC Action Plan helped bring about improvements in the situation on AMR that would not have happened otherwise. The majority of survey respondents (78 %) agreed with this (24 out of 134 responded 'strongly agree'; 80 out of 134 responded 'agree'). Specifically, the Action Plan was important for prioritising, coordinating and harmonising national activities at EU level (also discussed in Section 6.1) (INT2, INT3, INT12, INT21, INT23), although the challenge persisted that some Member States had taken more action to address AMR than others (INT4, INT17, INT18). Participants in the first stakeholder workshop explained that the Action Plan provided a guiding framework which enabled Member States to continue their ongoing efforts to tackle AMR and launch new initiatives. They also suggested that through its coordinating role and by encouraging activities to be more joined up, the Action Plan enabled more to be achieved than would have been achieved through similar actions done in a less coordinated way. Specific areas where significant progress was identified in coordination and harmonisation include the collection and reporting of monitoring and surveillance data (discussed in Section 4.2.3), the organisation of awareness campaigns related to EAAD (see Section 4.2.4), and national AMR research activities (see Section 4.1.3).

Research and innovation initiatives under the Action Plan improved coordination and encouraged collaboration across countries (as discussed in Sections 3.2 and 6.2). The ND4BB Drive AB project, which was funded by the IMI and involved public and private partners from 12 countries, was identified as one such example (INT2, INT3, INT18). The JPIAMR was another important achievement of the Action Plan in that it led to the creation of a strategic research agenda on AMR (JPIAMR 2013b), led to a mapping of AMR research funding in Europe (Kelly et al. 2015), and enabled improved coordination of national-level AMR research activities across countries (INT5, INT20 INT24; WHO 2015a). Two other interviewees, representing a European agency and an international organisation, described research in general as an area where there had been strong added value as a result of the Action Plan (INT13, INT21).

Activities under the Action Plan also helped achieve greater integration and harmonisation of monitoring, surveillance and reporting by European agencies through the ESVAC, EARS-Net and ESAC-Net systems (case study 5; INT2, INT3). Under action 10, a new legal framework for harmonised monitoring of AMR in zoonotic and commensal bacteria was introduced. The ECDC also launched a protocol (2014g) for harmonised monitoring of AMR in humans for *Salmonella* and *Campylobacter* isolates, which is expected to improve reporting standards in EU/EEA countries (Appendix N). When asked to identify specific activities that had been enabled by EU funds in a Member State that would not have occurred without that support (or would have occurred more slowly or to a lesser extent), 7 of 12 survey respondents mentioned surveillance and monitoring programmes. Interviewees also highlighted the Action Plan's role in coordinating monitoring and surveillance so that countries could produce comparable data (INT13, INT21), and two agency representatives (INT14, INT23) specifically cited improved comparability of animal and human data as a result of this integration: ECDC, EFSA and EMA were able to produce a joint report (2015), which analysed links between the consumption of antimicrobial agents and the occurrence of resistance.

7.2 Extent to which improvements in the situation on AMR could be associated with the EC Action Plan

Evaluation question 10: *To what extent can improvements in the situation on AMR (outcomes and other changes identified in the previous EQs) be associated with the development and implementation of the EC Action Plan?*

This evaluation question addressed whether progress made on AMR as identified in the findings from the preceding evaluation questions could be associated with the Action Plan. The judgement criterion focuses on whether there was observable progress — or no negative changes — in relation to the Action Plan objectives. The indicators assessed evidence of effective support being provided for research and innovation related to AMR, international collaboration and coordination, and improvement in policies and guidance relevant to AMR, and whether improvements could be associated with the Action Plan or the Action Plan was linked to any negative outcomes.

7.2.1. EU AMR policies and guidance were developed or improved

The Action Plan brought about the development of specific policies and guidance related to AMR, either through direct action at EU level or by stimulating the creation of national guidelines (as discussed in Sections 6.1 and 7.1). Actions under the Action Plan were associated with the development of specific policies and guidance relevant to AMR, including the new Animal Health Law, the Guidelines for prudent use of antimicrobials in veterinary medicine, and proposals for veterinary medicinal products and medicated feed (EC 2015c). As discussed in EQ3, the Animal Health Law proposal was adopted by the Commission and was undergoing the ordinary legislative procedure at the time of the evaluation. It expanded the legal basis for monitoring pathogens in animals and was viewed as an important step that was likely to be at least partly effective for preventing microbial infections and their spread (see Section 4.2.1). The proposals on veterinary medicinal products and medicated feed, which were undergoing the ordinary legislative procedure in the European Parliament and the Council at the time of the evaluation, were generally viewed as a positive step (see Section 4.1.2). The EU was also involved in international activities to control the spread of AMR, although there was limited evidence of the effectiveness of the activities and commitments (as discussed in Sections 4.2, 4.3 and 6.1).

7.2.2. Some improvements in the EU's AMR response were associated with the Action Plan

An important impact of the Action Plan was as a symbol of the EU's political commitment to tackling AMR (Section 7.1). It resulted in increased global awareness of AMR and contributed to international coordination efforts for addressing AMR. Multilateral and bilateral coordination occurred through TATFAR and with the OIE, the WHO, the Global Foodborne Infections Network, the OECD, the Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), the Codex Alimentarius Commission, China, the Russian Federation and the United States, among others (Section 4.1). These activities involved the development of recommendations, standards and guidelines and policy strategies, as well as conferences and other information exchange events. Several of these activities were set out under action 8, including cooperation with the OIE, the Codex Alimentarius Commission and TATFAR. An additional task under action 8, cooperation on the reduction of environmental pollution by antimicrobials, was also carried out (Section 6.2).

Some progress was made in improving public awareness about AMR and appropriate use of antimicrobials, and national campaigns contributed to raising awareness (Section 4.2). The Action Plan was linked with decisions to implement awareness-raising activities in some Member States (Section 4.2.4). The EC Action Plan helped to encourage Member States that had not implemented communication campaigns to do so (Section 6.1.1). Some national AMR awareness days were linked to European

Antibiotic Awareness Day, which acted as a general framework to mobilise some European countries to take action in this area (case study 6, Appendix N).

Another area of progress was in the consumption of antimicrobials for use in animals (as assessed by sales), but this change was not widely attributed to the Action Plan (Section 4.1.2). There was an overall decrease in antimicrobials sold, of 8 % (mg/PCU) on average, in the EU from 2011 to 2013 (the period for which data were available), although there was large variability in sales patterns across countries. Only 38 % of survey respondents said changes in sales could be attributed (at least in part) to the EC Action Plan, while 27 % said they could not be attributed (Section 4.1.2). Many survey respondents explained that such attribution would not be appropriate because national actions in this area had preceded the introduction of the Action Plan.

The Action Plan also resulted in improvements in monitoring and surveillance (Section 7.1), although it is acknowledged that performance across countries in this area remained variable. Systems for monitoring and surveillance of resistance were strengthened since introduction of the Action Plan in 2011 (Section 4.2). Specific progress involved the inclusion of a legal basis for monitoring AMR in animal pathogens in the new Animal Health Law (related to actions 5 and 10), improvements in reporting rules in Member States (introduced with support from ESVAC), increased use of standardised protocols and improvements in data quality and coverage (Section 4.2). Interagency analysis and reporting also developed during the period of the Action Plan, with joint reports on AMR in zoonoses being published by the ECDC and EFSA since 2011, and the first EFSA/ECDC/EMA joint report, published in 2015, which brought together data on consumption in humans and animals with data on occurrence of AMR (Sections 4.2 and 3.4).

Regarding the appropriate use of antimicrobials in humans, the Action Plan included an action that aimed to ensure that Member States effectively implemented existing recommendations on the prudent use of antimicrobial agents in human medicines. Overall, policies to address the use of antimicrobials in human medicine (which were the responsibility of Member States) improved in some areas, but it was too early to assess their impact on the occurrence of AMR or antibacterial consumption patterns (Section 4.1). There was no change in the consumption of antimicrobials for humans in the EU since 2011, although there was an undesirable shift towards increased use of broad-spectrum antibacterials (Section 4.1.1.3). Trends in the appropriate use of antimicrobials in humans were attributed to the Action Plan (at least in part) by just 14 % of respondents. Survey respondents again indicated that national policies played a more significant role, many of which had been introduced prior to 2011 (Section 4.1.1).

Overall, observed changes in various indicators related to AMR and how it was being addressed by Member States were challenging to attribute to the Action Plan because multiple initiatives were introduced prior to and in parallel with the Action Plan. The timelines for the Action Plan and this evaluation meant that there may not have been enough time for policy changes introduced in response to the Action Plan to bring about changes on the ground that could be captured in published data. Comments made by consultees in response to questions about the extent to which change could be attributed to the Action Plan underlined the fact that some Member States introduced measures to address AMR before the Action Plan was introduced — sometimes in response to a specific human or animal health issue that had arisen. International and regional initiatives, such as those initiated by the WHO in 2011 and publication of the WHO/Europe AMR Action Plan in 2011, are two additional examples of ongoing activities that could also have stimulated Member States to take action on AMR.

7.2.3. Significant support was provided to advance AMR-related research and innovation in the EU, but it was too early to assess research outcomes

Research and innovation support mechanisms were introduced at EU level in the period since 2011 to support research on AMR and promote innovation in antimicrobials and other treatments (Section 4.1), and the support provided was linked to the Action Plan. Many of these mechanisms related to specific actions under the Action Plan, including the ND4BB programme under the IMI (action 6), FP7 and Horizon 2020 funding (action 9), JPIAMR (action 9), and work to address uncertainties and a lack of incentives related to innovation in veterinary antimicrobials (action 7). EU funding represented a major source of public funding for AMR-related R&D globally in the period 2007-2013, and it supported basic science through to innovation in drugs, vaccines and rapid diagnostics (Section 5.1.1).

The Action Plan led to an increase in EU-level funding for research related to AMR (Section 5.1). In some cases, support was provided through mechanisms that predated the Action Plan, such as FP7, but the Action Plan resulted in focused and targeted allocation of research funding to AMR-related research under FP7, which continued under Horizon 2020 (Section 5.1.1). EU funding also helped leverage additional industry support through the IMI ND4BB programme (Section 4.2). A major part of EU research funding was the ND4BB programme, and the explicit inclusion of AMR in IMI2's strategic documentation was a direct impact of the Action Plan (INT5). The Commission also introduced more support through Horizon 2020 for research related to the JPIAMR as a result of the Action Plan (Section 4.1.3). Under action 7, a request was made for scientific advice from the EMA on how new veterinary antimicrobials might impact AMR. Increased coordination of research on AMR across countries occurred through the JPIAMR (Sections 5.1, 6.2 and 7.1).

One challenge for assessing the effectiveness of these measures was that the EU-funded (or co-funded) research projects which started from 2011 were generally ongoing at the time of the evaluation (Section 5.1.1). Moreover, even once they finish, it may take more than 10 years for their impacts to be realised (Morris et al. 2011). Thus, it was too early to evaluate the outcomes of the research projects funded. With regard to the Action Plan's specific objective of stimulating innovation in antimicrobials or alternatives for treatment, steps were taken to support work in this area since 2011 (Section 4.1.3). This included establishing new public-private collaborations under the IMI, funding research to explore business models that would decouple profits from the volume of drug sales, and efforts to address uncertainties that hinder innovation in veterinary antimicrobials (Section 4.1). Concerns persisted that there was a lack of incentives for veterinary antimicrobials innovation, but it was also acknowledged that this challenge remains an issue worldwide (Section 4.1.3.2).

8. CONCLUSIONS AND RECOMMENDATIONS

The Action Plan covered areas relevant to the needs for reducing the risks associated with AMR in the EU. It captured a 'one health' approach, bringing together actions to address animal health; human health; and, to a lesser extent, the environment.

Progress was made, to varying degrees, in the areas covered. Some observed improvements were associated with the Action Plan, and other Action Plan activities were expected to bring improvements in future. For instance, the EU also introduced policies and guidance in animal health that were expected to bring positive impacts for infection prevention and the appropriate use of antimicrobials in animals.

Significant progress was made in monitoring and surveillance. The coverage and scope of data collected by the EARS-Net, ESAC and ESVAC surveillance networks improved. Furthermore, Decision 2013/652/EC on monitoring and reporting of AMR extended the coverage and scope of data collected in zoonotic and commensal bacteria in food-producing animals and certain foods. Interagency collaboration also increased during the period of the evaluation, with a joint analysis by the ECDC, EFSA and EMA being published in 2015 that linked resistance and antimicrobial usage across humans and food-producing animals.

Variability was observed across Member States in terms of patterns of drug usage, occurrence of resistance, and the extent to which policies had been introduced and implemented to tackle AMR. This issue was a particular challenge in the areas related to human health, where Member States are responsible for action and EU competence is limited. Progress was attributed to the Action Plan to a lesser extent in stimulating Member States to develop AMR policies and run campaigns to raise public awareness. A small improvement in public awareness about AMR was observed during the evaluation period. Although data are available about patterns of antimicrobial usage and the occurrence of resistance in the EU, it was also too early to assess the role of the Action Plan in any observed trends.

Major developments in mechanisms to support and coordinate research and innovation were attributable to the Action Plan. It was too early to assess their longer-term outcomes for addressing AMR, but the EU increased its funding for AMR-related research, established AMR as one of the priority topics under the IMI flagship public-private partnership programme, and helped countries better coordinate their national-level AMR research programmes. Steps were also taken under the Action Plan to address challenges related to the innovation environment for development of new antimicrobials for patients and animals.

This section presents the conclusions that emerged from the evaluation findings against each criterion and related evaluation questions, and it presents recommendations.

8.1 Conclusions

This section presents the conclusions to the evaluation by criterion.

8.1.1. Relevance (EQ1)

To what extent do the objectives of the Action Plan address the problems identified in 2011? How well do these objectives still correspond to the current needs of tackling AMR in the EU?

There was a high degree of consensus about the issues that needed to be addressed to tackle AMR when the Action Plan was published in 2011, as evidenced by the similarity in issues identified across national and international reports and policy documents published around that time and the fact that most Action Plan objectives

were very relevant according to more than 70 % of the survey respondents. To a large extent, the Action Plan addressed these issues in its objectives, and all of the objectives in the Action Plan were relevant to the needs in 2011.

There were, however, three policy areas identified in other documents and reports at the time that the Action Plan was published that were not explicitly addressed in its objectives or that were covered to only a limited extent in the 12 actions. These areas were (i) actions for Member States to develop national plans or strategies; (ii) international cooperation on global monitoring of usage and AMR, as well as access to quality medicines, and vaccines, diagnostics and other health services; and (iii) environmental issues. In addition, while the Action Plan included three actions related to research and innovation, greater emphasis was placed on the development of new antimicrobials than on other areas. It is challenging to determine what the balance of R&D investment in this area should be, but there was some evidence to suggest that the Action Plan should have placed more emphasis on the development of vaccines, on diagnostics, and on other aspects of research related to AMR.

The issues addressed in the Action Plan remained relevant from 2011 to 2015. Indeed, many of the issues covered by the Action Plan's objectives increased in perceived relevance during that period — likely owing to wider growth in recognition of AMR as a serious global health threat that occurred during the same timeframe.

Needs that were identified in 2011 but not addressed explicitly by the Action Plan (or addressed only to a limited extent) also remained relevant. First, the EU guidelines for the prudent use of antimicrobials in veterinary medicine published in 2015 call for holistic strategies and/or action plans to be put in place. Second, the need to address global aspects of AMR emerged more strongly. Emergent issues relate to the quality of antimicrobials, global monitoring of usage and AMR, and ensuring access to quality antimicrobials — as well as vaccines, diagnostics and other health services. Third, evidence from 2015 indicated that the role of the environment in the spread of AMR needs to be further explored, and that this issue goes beyond pollution from drug manufacturing (which was addressed in the Action Plan). Further understanding of the transmission of AMR from animal husbandry, healthcare facilities and sewage treatment plants into water systems and soils is needed. Finally, there is a continued need for AMR-related R&D, including the development of new antimicrobials as well as vaccines, diagnostics and other treatments.

8.1.2. Relevance (EQ2)

Are the areas for EU action appropriate in view of the distribution of EU and national competences?

In total 84 % of survey respondents agreed or strongly agreed that the Action Plan identified actions that are best dealt with at EU level. Due to differences in the EU's competences in different sectors (e.g. with the EU having greater responsibility with respect to animal health issues and the Member States having greater responsibility on human health), the character of actions varied by sector. In animal health, where the EU has more competence, the associated actions (2, 3 and 5) focused on EU legislative action. Actions in human health (1 and 4) focused on promoting and monitoring Member State activities. Member States share responsibility with the EU for supporting research and innovation, and the associated actions centred on EU action to support research (6, 7 and 11), assist Member States and other countries with coordinating their AMR research programmes (11) and better understand the need for veterinary antimicrobials innovation (7). Other actions focused on EU actions in multilateral and bilateral cooperation (8), monitoring and surveillance systems (9 and 10) and monitoring of EU-level public awareness about AMR (12).

8.1.3. Effectiveness (EQ3)

To what extent have the actions been effective at improving treatment of infections in humans and animals?

The EU monitoring and surveillance systems regarding the consumption of antimicrobials in humans (ESAC) and animals (ESVAC) have been strengthened in both coverage and scope. Improvements occurred in the coverage and scope of data collected for the ESAC-Net network of national surveillance systems on antimicrobial consumption in humans. The ESVAC project, which gathers data on sales of antimicrobials for use in animals, achieved improvements in data harmonisation and increased data coverage, and ESVAC supported the development of rules requiring drug sellers to report sales figures.

However, it was not possible to attribute changes in consumption of antimicrobials for use in humans or animals to the Action Plan, for two reasons: (i) at the time of this evaluation, it was too early for changes attributable to the Action Plan to be observed and reported and (ii) effects of the Action Plan could not be disentangled from the effects of other AMR policy initiatives that were taking place prior to and in parallel with the Action Plan. Variability was observed across Member States in terms of patterns of drug usage in humans and animals. It was also too early to assess the impact and outcomes of research and innovation projects.

However, during the period of the Action Plan, improvements occurred in some policies for the treatment of infection in both humans and animals and in ensuring that those policies were supported by a better resourced and more targeted R&D effort.

In the area of human health, there was some improvement in national policies and performance related to AMR, in line with implementation of the Council Recommendation of 15 November 2001 on the prudent use of antimicrobials in human medicine (action 1), and the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections (action 4). The evaluation of both council recommendations has shown that areas for improvement include control measures in nursing homes and LTCFs, compliance with infection control guidelines in all settings, linking of national AMR action plans to HAI control strategies, and targeted surveillance of HAIs in LTCFs and other settings. Implementation of both sets of recommendations varied widely across Member States.

In the area of animal health, the Commission introduced guidelines in 2015 on prudent use of antimicrobials in veterinary medicine (action 3). European Commission proposals in 2014 on veterinary medicines and medicated feed covered the issues set out in the Action Plan (action 2) and were widely expected to produce improvements in this area. Both sets of measures could be directly attributed to the EC Action Plan. Measures similar to the European Commission guidelines introduced by some Member States had produced favourable impacts in terms of reductions in occurrence of AMR. The guidelines and legislative proposals that were introduced were widely expected to promote appropriate use of veterinary antimicrobials.

Research and development made up a significant part of the Action Plan; it was the overarching focus of two objectives and was addressed in the actions of a third (6, 7 and 11).

Research projects were supported primarily through the FP7 and Horizon 2020 framework programmes, and a framework agreement for public-private partnerships (including academia, SMEs and large pharmaceutical companies) was established under the IMI. Under the Action Plan, AMR became one of the IMI's 12 priorities. The ND4BB programme to spur the development of new antimicrobials for use in humans was established through the IMI, and ND4BB consists of seven projects.

It was too early to assess the effectiveness of funded projects in delivering new medical interventions, longer-term patient benefit or reductions in levels of resistance. The evidence that was available indicates that R&D initiatives resulting from the Action Plan led to increased support for AMR research as well as improvements in coordination (across countries through the JPIAMR and across the public and private sectors through the IMI). Conditions for more efficient R&D through open data sharing were created in the context of the ND4BB programme under the IMI, although there were some indications that this sharing should extend beyond the consortia involved in projects.

The Action Plan included measures to support antimicrobial innovation; for example, the EMA developed and presented guidance related to regulatory approvals for new antimicrobials, and research was funded to explore business models that would encourage antimicrobial development in light of the need to restrict antimicrobial use. Overall, progress in drug development was limited, but it was expected that progress in this area will take time. Despite actions under the Action Plan, a lack of incentives remained a barrier to innovation in antimicrobials for veterinary medicine.

Projects were funded in areas including developing antimicrobials and alternative infection treatments, diagnostics, preventive measures such as vaccines, and aspects of the prudent use of antimicrobials (including social aspects). Support was largely concentrated on the development of new antimicrobials. There was some evidence to suggest support should have been more evenly spread across the areas covered, but it is not possible to say what the ideal distribution would have been.

8.1.4. Effectiveness (EQ4)

To what extent have the actions aimed at containing the risks of spreading AMR been effective?

The EU monitoring and surveillance systems regarding the resistance of antimicrobials in humans (EARS-Net) have been improved (in both coverage and scope). Furthermore, Decision 2013/652/EC, on monitoring and reporting of AMR, has extended the coverage and scope of data collected in zoonotic and commensal bacteria (in food-producing animals and certain foods).

Changes in the occurrence of AMR in humans or animals could not be linked to the Action Plan because at the time of this evaluation, it was too early for changes attributable to the Action Plan to be observed and reported, and effects of the Action Plan could not be disentangled from the effects of other AMR policy initiatives that were taking place prior to and in parallel with the Action Plan. Variability was observed across Member States in terms of patterns of resistance in humans and animals.

However, the Action Plan played a role in activities aimed at containing the risks of spreading AMR. These encompassed the development of legislation and guidance, developing and fulfilling bilateral and multilateral commitments, enhancing surveillance and monitoring activities, and undertaking efforts to improve public awareness. Some progress was made in all of these areas, and this progress was linked to the Action Plan in many cases, with significant progress made in improving monitoring and surveillance systems in particular. Progress made centred on activities and short-term outcomes related to programme development and policy initiatives, rather than in longer-term changes in levels of AMR or other indicators.

The Action Plan's objective to put forward a proposal for a new Animal Health Law was met, with the proposal finalised and adopted by the European Parliament and Council in March 2016. The Law introduces the legal basis for monitoring antimicrobial resistance in animal pathogens and was viewed as an important step likely to be at least partly effective for preventing microbial infections and their spread.

The Action Plan contributed to the strengthening of monitoring and surveillance systems in the EU. The coverage and scope of data collected by EARS-Net improved. Decision 2013/652/EC, on monitoring and reporting of AMR, extended the coverage and scope of data collected in zoonotic and commensal bacteria in food-producing animals and certain foods.

Other notable progress in monitoring and surveillance concerned interagency collaboration: a 2016 EFSA and ECDC joint report published data collected on resistance in zoonotic and indicator bacteria for the first time under Decision 2014/652/EC, and EFSA, ECDC and EMA published a report in 2015 jointly analysing drug resistance and antimicrobial consumption in humans and food-producing animals. EU action linked to the Action Plan was credited with contributing to the observed progress in surveillance.

Several initiatives were undertaken related to international cooperation as part of the Action Plan, including multilateral commitments to control the spread of AMR. EU-supported AMR initiatives (such as the JPIAMR and EURL-AR) contributed to international projects. These included the WHO global Action Plan; the Global Foodborne Infections Network; OIE standards; TATFAR; the *Guidelines for Risk Analysis of Foodborne AMR* (part of the Codex Alimentarius); and work with the OECD, China and the Russian Federation.

European Antibiotic Awareness Day was credited with supporting pre-existing national campaigns and fostering the development of new campaigns, and it may have also helped raise awareness among policymakers and public health professionals. The Action Plan stated that EAAD (which was established three years prior to the introduction of the Action Plan) should be continued, but did not include it in an action. Very limited improvement was observed in public awareness about AMR across the EU, as measured by the Eurobarometer survey.

8.1.5. Effectiveness (EQ5)

To what extent has the coverage of actions across different services (DGs) within the European Commission been effective in capturing the holistic approach and in delivering results?

In total, 98 % of the survey respondents agreed with the need for a holistic approach, and 63 % believed that the EC Action Plan captured this holistic approach. The actions of the Action Plan addressed most sectors relevant to tackling AMR: human health, animal health, agriculture, and research and innovation. The plan also addressed cross-sectorial areas: international cooperation and public awareness about AMR. The environment was included in the Action Plan as a sub-action of action 8, which focused on the development and/or strengthening of multilateral and bilateral commitments in all sectors. However, environmental issues were addressed to only a limited extent, and this represented a shortcoming in the extent to which the 'one health' approach was captured.

The Action Plan was holistic in its objectives and the areas it covered, but it was viewed by some consultees as largely sector-specific in its implementation. Commission representatives reported that implementation of the Action Plan involved interaction among DGs. However, stakeholders and others reported a need for more cross-sector coordination and they to some extent lacked awareness of collaboration taking place within the Commission and with the agencies.

8.1.6. Efficiency (EQ6)

Has the EU budget been efficiently used to address the objectives of the Action Plan?

Information was available on EU research expenditure for AMR, but limited data were available for other Action Plan activities, which severely limited the potential to

provide a reliable quantitative assessment of the efficiency of the Action Plan. Furthermore, it was challenging to assess the impact of ongoing research and innovation activities, because it takes time before R&D efforts deliver results. Therefore, the analysis of efficiency focused on two core dimensions: (i) AMR research expenditure data and (ii) information from consultees and other sources about whether expenditures were justified.

EU funding for AMR-related research was primarily made available under FP7 (€1.08 billion), Horizon 2020 (€316 million through to the end of 2015) and the IMI programmes (€314 million). Additional resources were leveraged through IMI funding from the pharmaceutical industry and elsewhere (€382 million under the IMI). Apart from a small number of isolated expenditure figures, other areas of EU spending on the Action Plan were not available. The analysis also demonstrated that the EU agencies involved in AMR activities did not keep track of expenditure associated with AMR-related activities. Such accounting would have supported a higher level of transparency about expenditure on AMR and enabled a more comprehensive assessment of efficiency.

The expenditure on research was in line with the objectives of the Action Plan. Recent reports have emphasised the need for greater investment in R&D to tackle AMR globally and have highlighted EU funding as an important source of support. Moreover, EU sources accounted for a higher percentage of funding for research in AMR than they did for research overall, indicating that EU support constituted a valuable contribution to the AMR funding landscape. The research funding support provided through EU programmes was unlikely to have been made available otherwise.

The breakdown of this spending was strongly weighted towards therapeutics, reflecting the objectives of the Action Plan. However, evidence reviewed for this evaluation question and elsewhere in the report indicates there was a need to provide more support for other areas (e.g. understanding transmission, diagnostics, other interventions, surveillance and environmental issues).

8.1.7. Coherence (EQ7)

To what extent is the Action Plan coherent with Member States' relevant national (or regional) strategies and action plans and with similar initiatives at the international level?

The Action Plan was, on the whole, coherent with EU Member States' national strategies. It helped galvanise Member State action on AMR and influenced some national-level action plans (56 % of the Member State survey respondents) even though the EC Action Plan did not explicitly call on Member States to put in place national plans. In the survey, 61 % of Member State respondents said that their national plans and the EC Action Plan had a similar scope, and 26 % stated that the EC Action Plan had a broader scope. Relative to some national plans (e.g. Germany, the Netherlands, Norway and Switzerland), the EC Action Plan placed less emphasis on environmental issues.

EU collaboration with non-EU partners (the United States, Canada and Norway) was aligned with the EC Action Plan through TATFAR, and the EC Action Plan's actions were coherent with TATFAR activities. There was broad coherence in the EC Action Plan's objectives with the WHO (global and Europe) action plans; however, the WHO global Action Plan understandably places more emphasis on the need to develop capacity in human and animal healthcare in countries with more limited resources. The global Action Plan took the Commission- and JPIAMR-supported published research agenda as an example of the potential for a global initiative in this area.

8.1.8. Coherence (EQ8)

To what extent are the actions contained in the Action Plan coherent with other EU policies on the environment, human health, animal health and welfare, food safety, agriculture, research, competitiveness and SMEs?

According to the survey respondents, EU AMR policies complement or reinforce existing EU policies in the following areas: human health (78 % of respondents agreed or strongly agreed), animal health and welfare (80 % agreed or strongly agreed), food safety (75 % agreed or strongly agreed), research (77 % agreed or strongly agreed) and environment (56 % agreed or strongly agreed). EU policies were coherent with the actions in the EC Action Plan. Under actions 1 and 4, the Action Plan drew directly on EU recommendations from existing human health policies. Actions 9 and 12 complemented human health policy by supporting the collection of evidence that would inform relevant policies. Actions 2, 3 and 5 involved the development of EU animal health-related legislation and recommendations. Action 10, on strengthening surveillance systems, helped improve the evidence base for risk management related to animal health and food safety. Through its links to animal health and welfare and food safety, the EC Action Plan was consistent with EU agricultural policy. Under actions 6, 7 and 11, which covered aspects of research and innovation (including innovation by private industry), the Action Plan included activities that were consistent with EU policy on research, SMEs and competitiveness. Action 8 included activities related to all sectors, including the environment, and which were consistent with the relevant EU policies. While the Action Plan was not inconsistent with EU policy on the environment, it could have been more coherent if the breadth of its coverage of environmental issues had encompassed a wider range of issues, including the impacts of agricultural and human waste on AMR transmission.

8.1.9. Value added (EQ9)

What is the added value resulting from the EC Action Plan compared with what could be achieved by Member States at national and/or regional levels? Did the EC Action Plan identify the actions which should be best dealt with at EU level?

In the survey, the majority of respondents agreed that the EC Action Plan identified actions best dealt with at EU level (84 % agreed or strongly agreed). The Action Plan delivered added value for tackling AMR in two important ways. First, it acted as a symbol of EU political commitment and stimulated global and EU-level action on AMR. Second, it provided a framework to guide and coordinate national activities on AMR, enabling those activities to be more effective than they would have been without that coordination. Specific areas that benefitted clearly from improved international coordination were research and innovation, where coordination meant that national research funders could exchange information that would enable more strategic and effective research investment decisions, and monitoring and surveillance, where data collection and reporting across Europe became better harmonised, integrated and complete.

Value added (EQ10)

To what extent can improvements in the situation on AMR (outcomes and other changes identified in previous EQs) be associated with the development and implementation of the EC Action Plan?

The majority of survey respondents (78 %) agreed or strongly agreed that the EC Action Plan had helped bring improvements in AMR that would not have happened otherwise.

The Action Plan directly led to the development of EU policies and guidance that address AMR, including the new Animal Health Law, the *Guidelines for the Prudent Use of Antimicrobials in Veterinary Medicine*, proposals for veterinary medicinal products

and medicated feed, and the development of guidelines for prudent use in human health. The Action Plan was also linked to other progress made, in that it helped symbolise the EU's political commitment to tackling AMR, helped increase global awareness about AMR and contributed to international coordination efforts.

Significant progress was made in the harmonisation, integration, quality and coverage of monitoring and surveillance data on antimicrobial consumption and resistance across the EU. Improvements were largely linked to the Action Plan.

With regards to changes in the appropriate use of antimicrobials and resistance in both humans and animals, changes could not be linked to the Action Plan, for two reasons: (i) at the time of this evaluation, it was too early for changes attributable to the Action Plan to be observed and reported and (ii) effects of the Action Plan could not be disentangled from the effects of other AMR policy initiatives that were taking place prior to and in parallel with the Action Plan. It was too early to assess the impact and outcomes of research and innovation projects.

Some progress was made in improving public awareness about AMR. The EU's EAAD, an initiative that predated and was continued under the Action Plan, stimulated some Member States to organise awareness campaigns, although evidence linking increased awareness to such campaigns was limited.

EU funding represented a major source of public funding for AMR-related R&D globally, and it supported basic science through to innovation in drugs, vaccines and rapid diagnostics. EU action in this area under the Action Plan also entailed efforts to address the lack of incentives for veterinary antimicrobials innovation, which remained a challenge. An increase in EU funding targeted to AMR-related research and innovation activities was directly attributed to the Action Plan. While it was too early to assess the impact and outcomes of projects funded, the Action Plan led to relevant activities in this area, including public-private collaboration for antimicrobials innovation, coordination of research funding across countries, and exploration of business models that would promote antimicrobial innovation without incentivising increased drug consumption.

8.2 Recommendations

AMR remains a pressing problem, not only in the EU, but internationally. The Action Plan played an important role in symbolising and galvanising action on AMR issues within the EU and encouraged engagement with third countries and the international community to tackle AMR. In view of the importance of the issue and the EU's role as a leader in addressing these issues at a global level, the EU should build on progress already made and continue to play an active role in this area.

This section provides recommendations to be considered for future EU action on AMR.

8.2.1. Additional coordinated support should be provided to Member States

Member States require additional support to ensure that they can undertake the actions necessary to address AMR. A one-size-fits-all approach is insufficient, as the issues faced in different countries are diverse and success has been highly variable across Member States. Both funding and technical support are likely to be required for those countries lagging behind.

Future EU action could include a mechanism to encourage and support Member States in the development and implementation of national action plans on AMR. Such a mechanism could build on and bring together information gathered via current systems for monitoring and reporting on Member States' progress. This mechanism would encourage Member States to take a 'one health' approach to addressing AMR. Targeted attention could be paid to specific areas where a Member State is struggling

and to understanding the specific challenges that are blocking progress in that context. This mechanism could also encourage regional collaboration: EU Member States and third countries in Europe that are facing similar challenges could work together and share best practices.

8.2.2. The scope of environmental action should be expanded

The scope of environmental action should be expanded in future EU action on AMR. There is a need to improve scientific understanding of the role of the environment in the emergence and transmission of resistance through animal, human and manufacturing waste in water and soil, and to explore what action may be required to reduce associated risks. DG ENV should play a role in the design and implementation of future action in this area.

8.2.3. The EU should contribute further to international efforts

The EU should continue to work, in particular, with the WHO to determine the potential for supporting a global approach; this will help to address the potential risks of AMR spread associated with increased migration, tourism and trade. Given growing recognition of the need for a global understanding of AMR and of antimicrobial availability, quality and usage, the EU should strengthen existing international cooperation activities, in particular, with the WHO related to developing systems for global surveillance.

8.2.4. The EU should sustain support for research and innovation activities

AMR research and innovation activities are an important area and one where the EU has played an important role globally. Critical funding extended to research activities was catalysed by the Action Plan. The EU should sustain support for the projects and programmes that have been introduced. In collaboration with the JPIAMR, the Commission should also consider which topics should be covered by EU funding, in particular on research related to diagnostics, vaccines, alternatives to antimicrobials for treating infection, social and behavioural factors that drive antimicrobial usage, and the interplay between the environment and AMR.

8.2.5. The EU could expand its monitoring of AMR and of AMR-related activities

Improvements in monitoring and surveillance activities were a major success of the Action Plan. The EU could take a more holistic, data-driven approach to monitoring by linking data on resistance, consumption and sales of antimicrobials to prescribing trends and other factors — potentially extending to the environment. Such a system would provide a more complete picture of the AMR situation and help to pinpoint problem areas.

Specific targets and related indicators could be introduced, including, as appropriate, country-specific targets and indicators to ensure that information is being collected about progress on AMR issues related to shorter-term activities, outputs and outcomes in order to assist in assessing progress and linking this to longer-term outcomes and impacts. Targets related to longer-term indicators, such as usage of antimicrobials or occurrence of resistance, could also be considered.

More attention could also be paid on the cost-effectiveness of AMR policies. This would bring greater transparency about the costs and benefits associated with AMR policies within and outside the EU. It would also help inform international efforts to ensure that adequate financial investments are made to address AMR globally.

The Eurobarometer survey has provided an important source of data from across the EU on public awareness of AMR. This monitoring should continue to support awareness-raising activities through European Antibiotic Awareness Day.

8.2.6. The EU institutions and agencies could better communicate their efforts to stakeholders and the wider public

In line with the 'one health' approach, the Action Plan successfully brought together in one policy instrument actions related to animal health and welfare, food safety and human health. In implementing the Action Plan, the Commission and its agencies collaborated across DGs and agencies. While some collaborative activities, such as interagency reporting, were highly visible, external stakeholders were less aware of collaboration taking place within the Commission. The Commission and its agencies could better communicate to increase awareness about their cross-sectorial work and other activities, and their relationship to the Action Plan. Such communication would enable other countries and organisations to better learn from the approach being taken by the EU. This collaborative approach could also extend to encouraging interaction among stakeholders representing different sectors that are involved in addressing AMR but that historically have not interacted.

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