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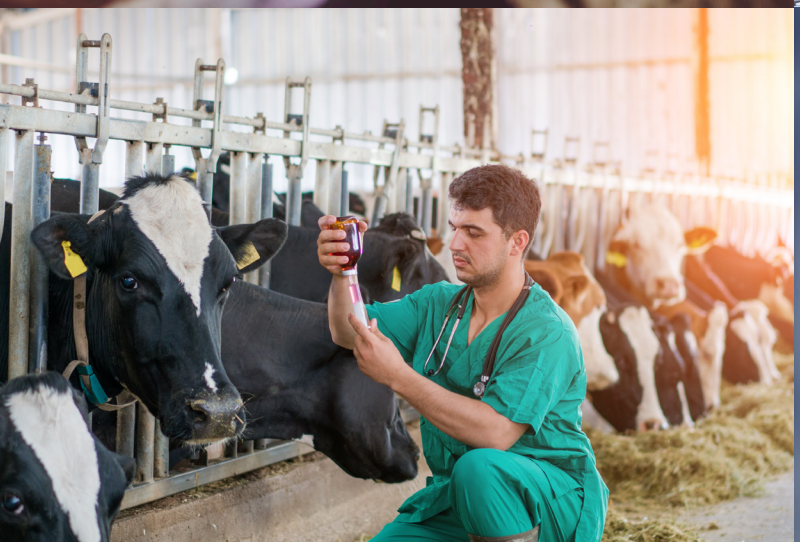

MANAGING ANTIMICROBIAL RESISTANCE ACROSS THE HEALTH SYSTEM

Opinion of the

Expert Panel on effective ways of investing in health (EXPH)

Health and Food Safety

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EXPERT PANEL ON EFFECTIVE WAYS OF INVESTING IN HEALTH

(EXPH)

Opinion on

Managing antimicrobial resistance across the health system

The EXPH adopted this opinion at the 13th plenary on 26 October 2022
after the public hearing held on 20 June 2022

About the Expert Panel on Effective Ways of Investing in Health (EXPH)

Sound and timely scientific advice is an essential requirement for the Commission to pursue modern, responsive and sustainable health systems. To this end, the Commission has set up a multidisciplinary and independent Expert Panel which provides advice on effective ways of investing in health (Commission Decision 2012/C 198/06).

The core element of the Expert Panel's mission is to provide the Commission with sound and independent advice in the form of opinions in response to questions (mandates) submitted by the Commission on matters related to health care modernisation, responsiveness, and sustainability. The advice does not bind the Commission.

The areas of competence of the Expert Panel include, and are not limited to, primary care, hospital care, pharmaceuticals, research and development, prevention and promotion, links with the social protection sector, cross-border issues, system financing, information systems and patient registers, health inequalities, etc.

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ABSTRACT

The current Opinion first explores the global and European impact of AMR. It offers an extensive analysis of factors contributing to its spread thereby highlighting the role of humans as well as animals and the environment: the One Health concept. It offers a comprehensive conceptual model of how AMR could be tackled in human health taking into account the multiple determinants of AMR which comprise the prescriber and patient characteristics, the health care system and the broader clinical culture. Practical strategies to fight AMR in human health should achieve the following outcomes: reducing the number of infections, decreasing the use of antimicrobials, and developing (rapid) diagnostic tests and antibiotics. We describe innovations and emerging technologies that offer promising possibilities.

In the second part, the Opinion analyses current AMR policies starting with the 2015 WHO Global Action Plan (GAP). The GAP consists of five key recommendations on which the 2017 EU One Health AMR Action Plan (with three pillars and fifteen objectives) is based. Although most EU countries have a national action plan (NAP), too few are fully implemented, often due to a lack of budget and/or capacity. The Commission and ECDC's AMR 'One Health' country visits provide expert advice & reports with country-specific recommendations that allow member states to share knowledge about causes of failure and how to implement NAPs. The WHO and the EU have developed several initiatives to collate evidence of effectiveness and provide member states with guidance on implementation of national plans. Still, many challenges remain.

The Opinion concludes by formulating five recommendations to the EU and member states for tackling AMR. We fully endorse the EU 2017 One Health Action Plan against AMR and our recommendations, which build on it, are: 1) All member states should ensure that they have comprehensive, up-to-date National Action Plans to tackle AMR and robust governance arrangements in place to implement them. 2) While recognising the different competencies given to the European Union by the Treaties in the areas of human and animal health, we recommend that the European Commission be more ambitious in taking advantage of the opportunities that exist to bring the two together, consistent with the concept of One Health. 3) The European Commission should prioritise the development of a comprehensive set of indicators and structured data to measure progress on tackling AMR, ensuring that they are integrated with relevant regulatory data collection requirements. 4) Member states should focus research on understanding why policies and practices on their territories continue to create risks of AMR and the European Commission should support exchange of the knowledge thus generated. 5) The European Commission should conduct a foresight exercise to inform future policy on AMR.

Keywords: Expert Panel on Effective Ways of Investing in Health, public health, antimicrobial resistance, One Health

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The current Opinion first explores the global and European impact of AMR. It offers an extensive analysis of factors contributing to its spread thereby highlighting the role of humans as well as animals and the environment: the One Health concept. It offers a comprehensive conceptual model of how AMR could be tackled in human health taking account of the multiple determinants of AMR which comprise the prescriber and patient characteristics, as well as the health care system and the overall cultural system. Effective strategies to fight AMR in human health should aim for one of the following outcomes: reducing the number of infections, decreasing the use of antimicrobials, developing (rapid) diagnostic tests or developing new antibiotics. Innovations and emerging technologies offer many promising possibilities.

In a second part the Opinion analyses the current AMR policies starting with the 2015 WHO Global Action Plan (GAP). The GAP consists of five key recommendations on which the 2017 EU One Health AMR Action Plan (with three pillars and fifteen objectives) is based. Although most EU countries already designed a national action plan (NAP), the main problem is the lack of implementation often due to a lack of budget and/or capacity. The Commission and ECDC's AMR 'One Health' country visits provide expert advice and reports with country specific recommendations which allow member states to learn from each other about causes of failure and how to succeed in implementing NAPs. The WHO and the EU developed several initiatives to summarize evidence of effectiveness, and to provide Member States with guidance and strategies to improve implementation of national plans in the member states. Still many challenges remain.

The Opinion concludes by formulating five recommendations to the EU and member states for tackling AMR. These recommendations fully endorse and build on the EU 2017 One Health Action Plan against AMR. They are based on the Opinion's conceptual framework of policy interventions at the health care system level. Those five recommendations are:

Recommendation 1: All member states should ensure that they have comprehensive, up-to-date National Action Plans to tackle AMR and robust governance arrangements in place to implement them.

Recommendation 2: While recognising the different competencies given to the European Union by the Treaties in the areas of human and animal health, we recommend that the European Commission be more ambitious in taking advantage of the opportunities that exist to bring the two together, consistent with the concept of One Health.

Recommendation 3: The European Commission should prioritise the development of a comprehensive set of indicators and structured data to measure progress on tackling

AMR, ensuring that they are integrated with relevant regulatory data collection requirements.

Recommendation 4: Member states should focus research on understanding why policies and practices on their territories continue to create risks of AMR and the European Commission should support exchange of the knowledge thus generated.

Recommendation 5: The European Commission should conduct a foresight exercise to inform future policy on AMR.

MANDATE

EU action on antimicrobial resistance (AMR) has been on the policy agenda for many years. A wide range of measures has been put in place to fight AMR and promote more prudent and responsible use of antimicrobials in humans and animals. It is important to note that AMR is a cross-sectoral issue and needs to be addressed at all levels and across all of the One Health dimensions, acknowledging the interlinkages between humans, animals, plants and the environment.[1]

Commissioner Kyriakides was mandated by the Commission President to focus on the full implementation of the European One Health Action Plan against Antimicrobial Resistance[1] and to work with our international partners to advocate for a global agreement on the use of and access to antimicrobials.[2] The Commission actively engages with international partners like the AMR Quadripartite Alliance [World Health Organization (WHO), Food and Agriculture Organisation (FAO), World Organisation for Animal Health (WOAH, founded as OIE), and United Nations Environment Programme (UNEP)], as well as G7 and the G20 to address the AMR threat. In particular, it advocates for the revision of the 2015 AMR Global Action Plan and supports inclusion of AMR in the global agreement on pandemic preparedness and response on which the World Health Assembly agreed to launch negotiations on 1st December 2021.

In June 2017, the European Commission adopted the EU One Health Action Plan against AMR.[3] Under the plan, the Commission adopted the EU Guidelines on the prudent use of antimicrobials in human health.[4] The guidelines aim to reduce inappropriate use and promote prudent use of antimicrobials in people. They target all actors responsible for or play a role in antimicrobial use. This complements the EU Guidelines on the prudent use of antimicrobials in animal health.[5] The European Medicine Agency (EMA), the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC) are all engaged in tackling AMR.[6-8]

Since the implementation of the 2017 AMR EU Action Plan, new policy initiatives have been launched that reinforce action on AMR, for example:

- The new EU Regulation on veterinary medicines and medicated feed came into force on 28th January 2022. It provides for a wide range of concrete measures to fight AMR and promote prudent and responsible use of antimicrobials in animals.
- In May 2020, the European Commission adopted the Farm to Fork Strategy, a tool to help shape the EU's path towards sustainable food systems.[9] It includes an objective to reduce by 50% of the overall EU sales of antimicrobials for farmed animals and in aquaculture by 2030.
- In November 2020, the Commission proposed legislative changes to the existing EU health security framework as part of the European Health Union package,[10]

including strengthening of the mandates of ECDC and EMA and the creation of the European Health Emergency Preparedness and Response Authority (HERA). HERA was established on 16 September 2021,[11] notably to promote the development and availability of medical countermeasures. On 12 July 2022, the HERA Board agreed on a list of top-3 health threats to prepare against, which includes AMR.

- Also as part of the European Health Union, the Commission adopted the Pharmaceutical Strategy for Europe,[12] under which the Commission will explore new types of incentives for innovative antimicrobials and consider in the review of the pharmaceutical legislation to introduce measures to restrict and optimise the use of antimicrobial medicines. Moreover, the strategy will also cover actions on improving healthcare professionals' and European citizens' awareness on antimicrobial resistance.
- In November 2020, the new Commission Implementing Decision (EU) 2020/1729 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria was published.[13] This Decision is based on the latest scientific opinions and addresses known implementation issues while scientifically responding and ensuring continuity in assessing future trends in AMR.
- In March 2019, European Union Strategic Approach to Pharmaceuticals in the Environment COM (2019) 128 final was adopted which covers also the antimicrobial resistance in the environment.

Almost all EU countries have put in place One Health national action plans and strategies on AMR[14] and, twice a year, the European Commission issues a progress report[15] on the implementation of the 2017 European One Health Action Plan against AMR.[1]

There is a wealth of research and studies available on AMR, commissioned by the European Commission and other national and international organisations.[16] For example, the Organization for Economic Cooperation and Development (OECD) has been providing an important contribution to the understanding on the economic side of the burden of AMR and the cost to health systems.[17] According to ECDC, 75% of the health burden of AMR in the EU/EEA is due to health care associated infections, while nearly 40% of the health burden of AMR is caused by infections with bacteria resistant to last-line antibiotics such as carbapenems and colistin.[18] The Council Conclusions on the next steps towards making the EU a best practice region in combatting antimicrobial resistance of June 2019 recognised the need for more action across several areas.[19]

Despite these developments, there are still challenges in effective implementation of AMR policies across health systems. This in part reflects the complexity of AMR: involving a wide range of pathogens; requiring concerted efforts at all levels; and engaging with stakeholders that include, but are not limited to: physicians, nurses, pharmacists, microbiologists, hospital managers, policy-makers, and patients.

The Commission considers that there is a need for a systematic approach that considers the health system as a whole, looking at institutional, behavioural and structural challenges and opportunities, something that does not seem to have been covered in existing studies so far.

However, the issues that need to be considered go far beyond the health system. AMR is a good example of a One Health issue in which human health is connected to that of animals and the environment. As a result, health systems both contribute to the emergence and persistence of AMR in the environment and are impacted by it. However, knowledge gaps still exist in understanding the environmental aspects of AMR and its relevance to health systems. The 2017 EU AMR Action Plan has various projects addressing this issue [One Health European Joint Programme (EJP), Ecology from Farm to Fork Of microbial drug Resistance and Transmission (EFFORT), Joint Programming Initiative on AMR (JPIAMR), 3rd ERA-NET Co-fund)].[15] In addition, EFSA recently adopted an opinion on "Role played by the environment in the emergence and spread of antimicrobial resistance (AMR) through the food chain" following a self-mandate.[20]

The **target audience** for this Opinion are EU institutions, national governments (including all relevant ministries, such as health, agriculture, the environment, and consumer protection) and as well as other stakeholders outside government. The scope is EU rather than global action. Given the limited competence in health, the Opinion should differentiate between action that can be taken at EU and at Member State levels.
The findings and recommendations of the Expert Panel Opinion will feed into a new proposal for a Council Recommendation on AMR to be issued later in 2022.

Questions for the Expert Panel

The Expert Panel is requested to provide a concise policy-oriented Opinion with analysis and recommendations on the following points:

1. Taking into account the One Health dimension of antimicrobial resistance (AMR), including the role of the environment and of veterinary medicine in the emergence and spread of AMR, what are necessary systemic[1] elements, conditions and interventions of effective management of antimicrobial resistance (AMR) across, but also beyond, the health systems that could translate into effective policy interventions and National Action Plans (national and EU targets, core requirements for antimicrobial stewardship and infection prevention and control standards, etc.)?

[1] This should include the whole health system – from prescriptions, to information for patients, infection prevention and control measures as well as other preventive measures, the structures and resources of health care systems, antimicrobial stewardship measures, and legislation that prevents sales of antibiotics 'over the counter' without a prescription

2. How might new technologies (e.g., digital apps, in vitro diagnostics) help tackle AMR in health systems?
3. Taking also into account the existing studies (e.g. those by OECD and ECDC) on the burden of diseases, where are the areas for most urgent investment across health systems for maximum benefit to tackle AMR?
4. What concrete strategies can be recommended to Member States to implement existing and planned policies to tackle AMR?

OPINION

1. Antimicrobial Resistance (AMR) and its impact

1.1. AMR

As defined by the World Health Organization, "Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severe illness and death. AMR genes refer to the genes implicated in or associated with the resistance to one or more antibiotics. Resistance can result from presence or absence of a gene or specific mutations acquired spontaneously or through evolution over time. As a result of drug resistance, antibiotics and other antimicrobial medicines become ineffective and infections become increasingly difficult or impossible to treat".[21] These changes are, mostly, as a result of spontaneous mutations that give the microorganism an evolutionary advantage, for example when that mutation confers resistance to an antibiotic in an environment where the microorganism is exposed to it.

Resistance is important because it threatens the progress that has been made with a succession of antimicrobials; in effect there is a constant race between the ability of humans to discover new antimicrobial agents and the microorganisms to acquire resistance to them. Ultimately, this creates the risk that medicine could revert to the pre-antimicrobial era, with profound implications for the management of infections and the ability to undertake procedures that increase their risk, such as surgery inside body cavities. It is not an exaggeration to say that the growth of AMR threatens the entire medical system as it exists today. The WHO has identified AMR as one of the top 10 global public health threats facing humanity.[21] The Commission's Directorate-General Health Emergency Preparedness and Response (HERA) includes AMR as one of the top 3 health threats that require coordination of measures at EU level in the context of medical countermeasures.[22]

AMR is now recognised as a major contributor to disease burden and one of the greatest threats to human health in the future. Quantifying this burden is complicated. Data from many parts of the world, including many high-income countries, are missing or incomplete. Estimates must also address the issue of attribution, deciding when a resistant bacterial infection causes death or disability. Consequently, estimates from different sources vary. However, the most comprehensive picture worldwide comes from a recent study by the Global Burden of Disease programme. This combined data from a wide range of sources, including surveillance networks, diagnostic laboratories, research studies, and health facilities and used modelling techniques to estimate missing data. Their approach included five components: number of deaths where infection played a role, proportion of infectious deaths attributable to a given infectious syndrome,

proportion of infectious syndrome deaths attributable to a given pathogen, the percentage of a given pathogen resistant to an antibiotic of interest, and the excess risk of death or duration of an infection associated with this resistance. Recognising the challenge of attribution noted above, they adopted a pragmatic solution by employing two counterfactuals, deaths attributable to AMR (based on a scenario in which all drug-resistant infections were replaced by drug-susceptible infections), and deaths associated with AMR (based on a scenario in which all drug-resistant infections were replaced by no infection).

Using these two counterfactuals, they estimated that 4.95 million (95% uncertainty interval (UI) 3.62–6.57 million) deaths globally were *associated* with bacterial AMR in 2019 and 1.27 million [95% UI 0.911–1.71] deaths were *attributable* to it. [23] Whichever measure is used, AMR caused more fatalities than HIV/AIDS or malaria, which caused 860,000 and 640,000 deaths respectively in the same year.

Looking beyond the aggregate figures, the authors looked at both the organisms (and agents to which they were resistant) and the types of infections they caused.

The Global Burden of Disease study presented data by organism and type of infection (categorised as a set of syndromes). In 2019, six pathogens were each responsible for more than 250,000 deaths globally *associated* with AMR: *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa*, listed in order of number of deaths. Together, these six pathogens accounted for 929,000 (95% UI 660,000–1,270,000) of the 1.27 million deaths (95% UI 0.911–1.71 million) *attributable* to AMR and 3.57 million (95% UI 2.62–4.78 million) of the 4.95 million (95% UI 3.62–6.57 million) associated with AMR globally in 2019. Six other pathogens were each responsible for between 100,000 and 250,000 deaths *associated* with AMR: *Mycobacterium tuberculosis, Enterococcus faecium, Enterobacter spp., Streptococcus agalactiae (group B Streptococcus), Salmonella Typhi,* and *Enterococcus faecalis*. For deaths *attributable* to AMR, E coli was the most important, followed by *K. pneumoniae, S. aureus, A. baumannii, S. pneumoniae*, and *M. tuberculosis*.

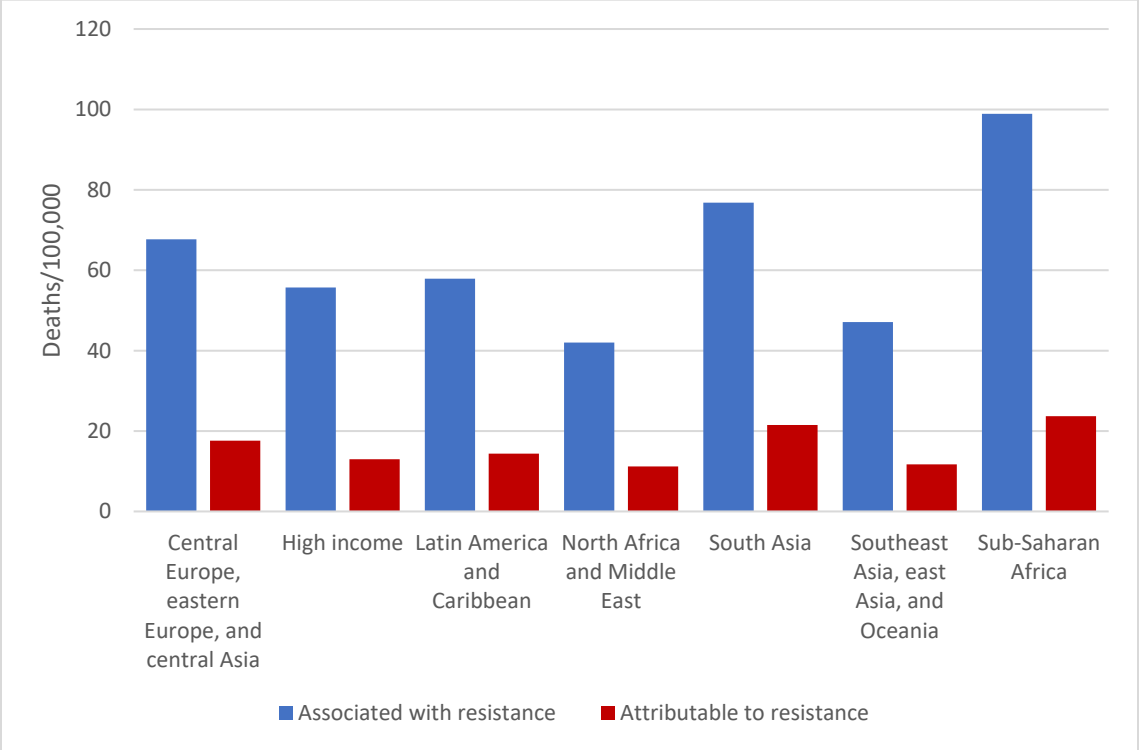
Three infectious syndromes dominated the global burdens attributable to and associated with AMR. These were lower respiratory and thorax infections, bloodstream infections, and intra-abdominal infections. Combined, they accounted for 78.8% (95% UI 70.8–85.2%) of deaths attributable to AMR 2019. Consequently, measures to reduce the number of these infectious syndromes and the risk of resistance associated with them are likely to be most effective in reducing the burden of AMR.

There are large geographical variations in the scale and nature of deaths (**Figure 1**) and Disability Adjusted Life Years (DALYs; **Figure 2**) associated with or attributable to AMR. Note that the Global Burden of Disease uses regions defined by a mix of geographic and economic characteristics. Thus, the High-Income region includes, alongside western

Europe, Australia, New Zealand, the USA, Canada, and countries in the lower cone of South America and in East Asia. Central and Eastern Europe includes the post-2004 EU member states (except Malta and Cyprus).

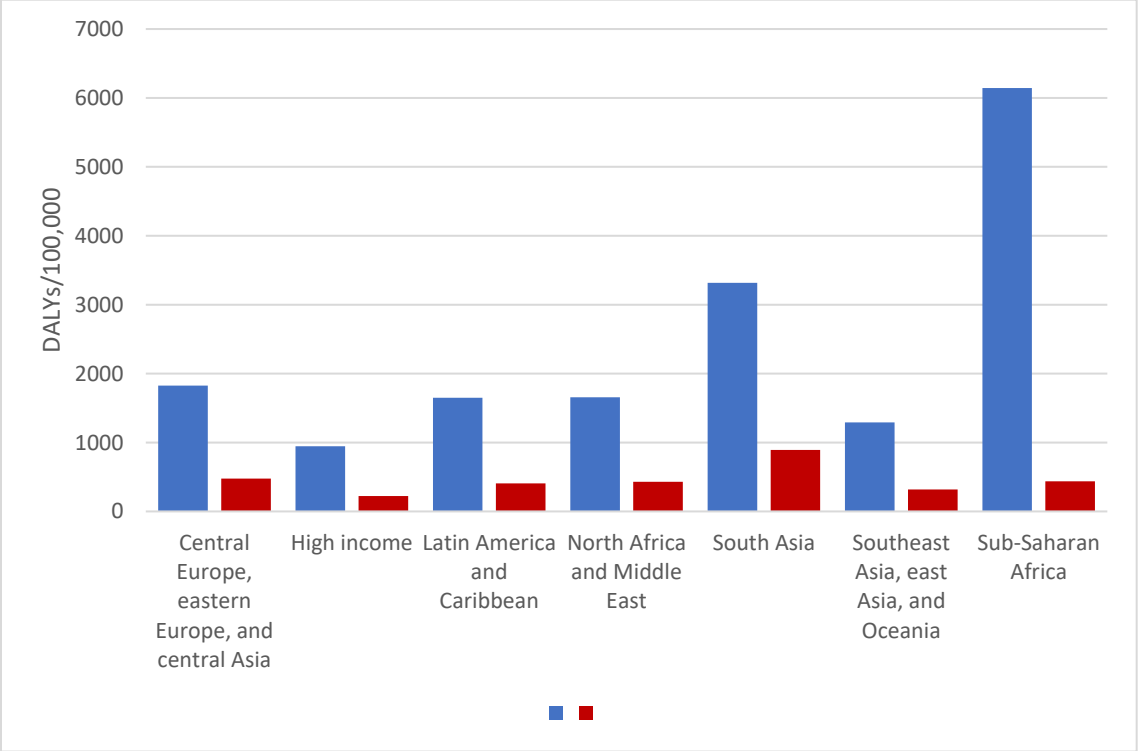
The disease burden is greatest in sub-Saharan Africa and South Asia, at 24 deaths per 100,000 population and 22 deaths per 100,000 population, respectively. Western sub-Saharan Africa had the highest rate of deaths attributable to AMR, with 27.3 deaths per 100,000 population. However, there is considerable variation within these regions.

Figure 1 All-age rate of deaths per 100,000 population associated with and attributable to bacterial antimicrobial resistance by region, 2019



Source: Murray et al., 2022[23]

Figure 2 All-age rate of disability-adjusted life years (DALYs) per 100,000 population associated with and attributable to bacterial antimicrobial resistance by GBD region, 2019



Source: Murray et al., 2022[23]

1.1.1. AMR in Europe

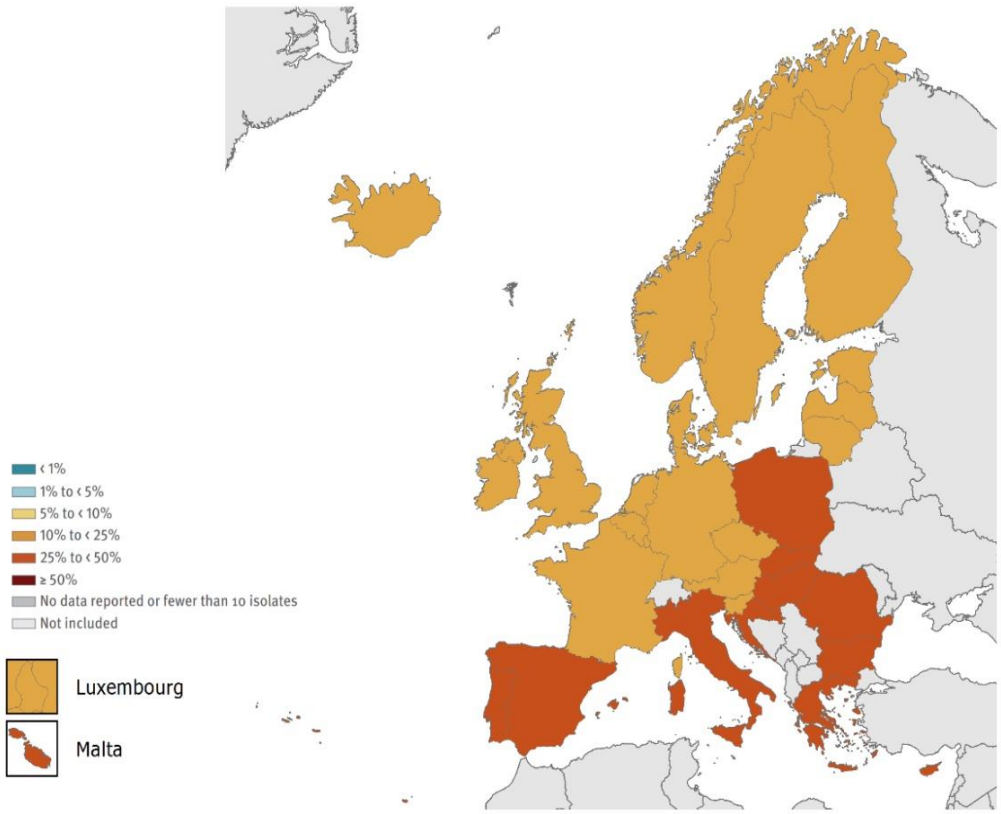
ECDC and the WHO Regional Office for Europe collaborate to publish data from antimicrobial resistance surveillance in Europe and obtained from invasive isolates (blood and cerebrospinal fluid).[24] The most recent data cover the year 2020. Although there are differences among countries in terms of the microorganisms involved and the antimicrobial groups to which they are resistant, it is possible to extract a few headlines. First, within the EU/EEA, most reported bacterial species–antimicrobial combinations showed either a significantly decreasing time trend or no significant trend in population-weighted mean AMR percentage during 2016–2020. The exceptions were carbapenem resistance in *Escherichia coli* and *Klebsiella pneumoniae* and vancomycin resistance in *Enterococcus faecium*, which saw a significant increase during this period.

By 2020, more than half of *E. coli* isolates and more than a third of *K. pneumoniae* isolates were resistant to at least one antimicrobial group, and combined resistance to several antimicrobial groups was frequent. Carbapenem resistance remained rare with *E. coli*, but almost a quarter of EU/EEA countries reported carbapenem resistance percentages above 10% for *K. pneumoniae*. Carbapenem resistance was also common with *Pseudomonas aeruginosa* and *Acinetobacter* species and at a higher percentage than with *K. pneumoniae.*

There was a reduction in the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) during 2016−2020 but MRSA remains of concern, with high percentages in several countries including Spain, Portugal, Italy, Austria, and Romania, and combined resistance to another antimicrobial group is common. There was a downward trend in macrolide resistance in *Streptococcus pneumoniae* during 2016-2020.

There is a clear north-to-south and west-to-east gradient of AMR in the EU/EEA, with higher rates observed in the southern and eastern parts of the Region.[25] The gradient was more pronounced for fluoroquinolone resistance in *E. coli*, (**Figure 3**), third-generation cephalosporin and carbapenem resistance in *K. pneumoniae* and carbapenem resistance in *Acinetobacter* species.

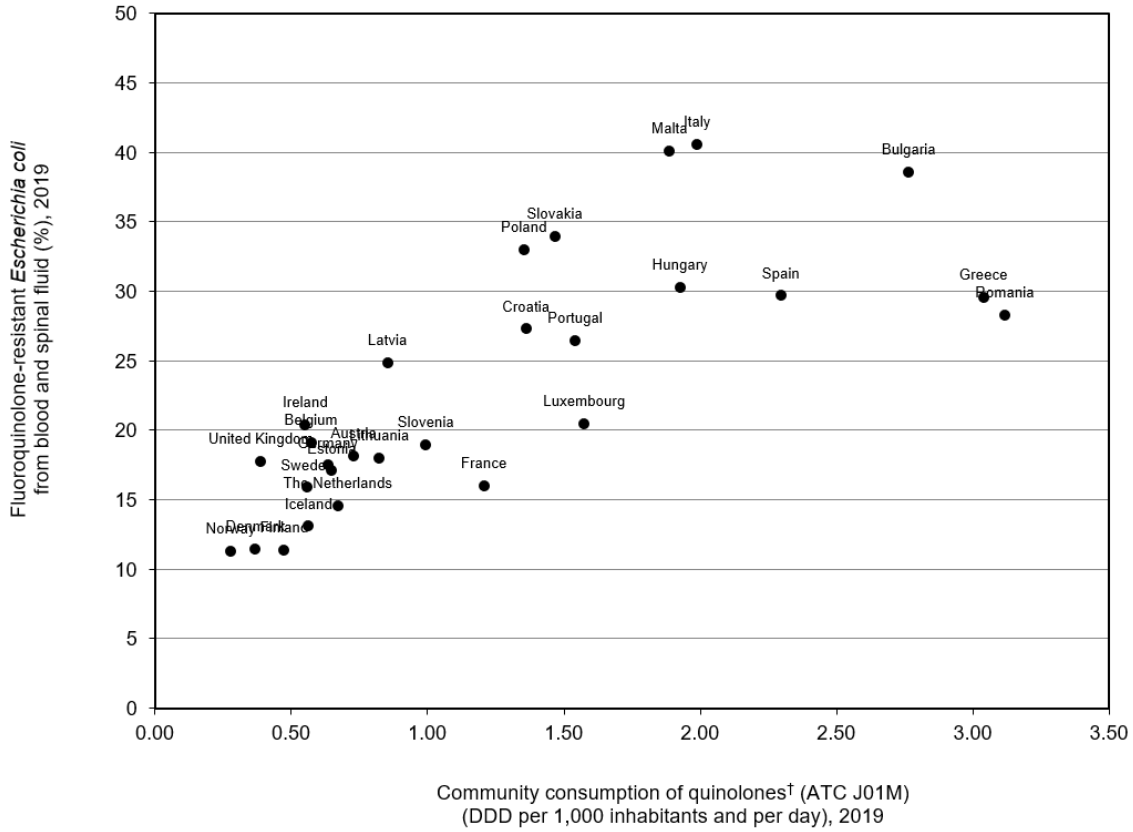
Figure 3 Percentage of invasive E. coli *isolates resistant to fluoroquinolones (ciprofloxacin or/and levofloxacin or/and ofloxacin), by country, EU/EEA, 2019*



Source: European Antimicrobial Resistance Surveillance Network (EARS-Net), ECDC [26]

The pattern seen in **Figure 3** reflects antimicrobial consumption rates, as can be seen from a plot of rates of fluoroquinolone-resistant *E. coli* and quinolone consumption (**Figure 4**). This is consistent with a 2014 systematic review finding a clear association between antibiotic consumption and rates of resistance.[27]

Figure 4 Association between use of and resistance to fluroquinolones in 28 EU/EEA countries (2019)



Source: EARS-Net and European Surveillance of Antimicrobial Consumption Network (ESAC-Net), ECDC, 2020.

Note: Each dot represents an EU/EEA country. *Excluding Cyprus and Czechia which only reported antibiotic consumption data for the community and hospital sector combined. †, Mostly fluoroquinolones. ATC, Anatomic Therapeutic Chemical classification code; DDD, defined daily doses

1.1.2. Antibiotic consumption in Europe

Antimicrobial consumption in the EU/EEA is monitored by ECDC for humans and by the EFSA and EMA for food-producing animals. In 2018, in 29 EU/EEA countries, 4,264 tonnes of antibiotics were used in humans, corresponding to a mean antibiotic consumption of 133 mg of active substance per kg estimated biomass, whereas 6,358 tonnes of antibiotics were used in food-producing animals corresponding to a lower mean antibiotic consumption of 105 mg per kg estimated biomass.[28] "Although the overall quantities of antibiotic used (in tonnes) are higher in animals than in humans, the mean antibiotic consumption rate (per kg estimated biomass) is lower in animals than in humans."

There is, however, a recognition of the need to reduce, as far as possible, the use of antibiotics. A particular target is their use in agricultural animals and there has been a 43% decrease in use between 2011 and 2020 in the 25 countries with consistent

reporting. However, there was little change in the antibiotic consumption in humans.[29] In animal health, antibiotics have been deliberately used in the past for reasons other than to treat disease, such as growth promotion. In the EU, growth promotion with antibiotics as part of feed was banned in 2006 and the 2019 Veterinary Medicinal Products Regulation banned it completely as of 2022, alongside several other measures.[30]

In 2019, the mean total (community and hospital sector combined) consumption of antibacterials for systemic use in humans in the EU/EEA was 19.9 defined daily doses (DDD) per 1,000 inhabitants per day (country range: 9.5–34.1).[31] (**Table 1**)**.** Most (approximately 90%) antibiotic consumption in humans takes place in the community, although the proportion of patients receiving an antibiotic on a given day is much higher in acute care hospitals (EU/EEA: 31% or 460 DDD per 1,000 patients per day) than in the community.[32]

During the period 2011–2019, a decreasing trend in total antibiotic consumption was apparent in the EU/EEA overall, with large reductions in some countries (**Table 1**). Yet despite these overall reductions, the relative use of broad-spectrum antibiotics, having an antimicrobial spectrum which includes some gram-positive and some gram-negative organisms, in humans increased,[31] and the remaining variability across countries show that further reductions are possible.

Table 1 Total consumption (community and hospital sector combined) of antibacterials for systemic use (ATC group J01) by country, EU/EEA, 2010–2019 (expressed as DDD per 1,000 inhabitants per day)

Country	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Netherlands	10.9	11.0	10.9	10.5	10.3	10.4	10.1	9.8	9.7	9.5
Austria	13.1†	12.7†	12.2†	14.2†	12.1†	12.1†	11.4†	11.9†	10.4†	11.4
Germany	13.4†	13.1†	13.7†	14.5†	13.4†	13.1†	12.8†	12.3†	11.9†	11.4†
Estonia	11.4	12.4	12.2	12.0	11.9	12.1	12.0	11.6	11.8	11.8
Sweden	15.2	15.4	15.3	14.2	14.0	13.5	13.2	12.8	12.4	11.8
Slovenia	13.4	13.4	13.2	13.3	13.1	13.3	13.0	13.1	13.2	13.0
Latvia	12.6	12.9	12.9	13.3	12.6	13.1	12.9	13.9	13.3	13.9
Hungary	14.8	14.9	14.1	14.5	15.2	15.8	14.4	14.6	14.8	14.4
Finland	19.7	21.5	20.6	19.6	19.1	18.1	17.4	15.7	15.5	14.7
Norway	16.8	17.5	17.9	17.2	16.9	16.8	16.2	15.7	15.3	14.9
Denmark	17.5	18.3	17.4	17.5	17.1	17.5	17.0	16.2	15.6	15.3
Lithuania	14.4	15.5	15.3	17.1	15.1	15.8	16.6	16.6	16.3	16.1
Czechia	16.0†	16.5†	15.7†	16.9†	17.1†	17.4†	na	na	na	16.9
Croatia	18.8	18.2	20.0	19.2	19.4	19.7	18.7	18.6	18.8	18.8
United Kingdom	16.5†	16.5†	17.7†	20.4	20.8	20.1	19.7	19.3	18.8	18.8
Slovakia	na	21.4†	19.7	23.2	21.2	24.2	23.6	20.0	22.0	19.3
Portugal	19.9	20.6	20.1	17.6	18.0	18.8	19.0	18.3	18.6	19.3
EU/EEA*	**20.9**	**20.9**	**21.0**	**21.5**	**21.1**	**21.5**	**20.7**	**20.2**	**20.1**	**19.4**
Iceland	19.8	19.8	19.7	19.4	17.1†	17.6†	18.2†	18.8†	20.4†	19.5†
Bulgaria	17.2	18.3	17.4	18.6	20.0	20.1	19.2	20.5	21.0	20.7
Malta	19.9	21.6	20.8	22.2	22.4	21.2	20.9	22.6	20.9	20.7

Luxembourg	25.1	25.2	25.0	25.0	23.2	23.5	22.9	22.6	22.2	21.1
Belgium	24.9	25.4	25.6	24.2	24.0	24.4	24.2	22.8	22.3	21.4
Italy	24.9	25.1	24.6	25.2	24.5	24.5	24.0	20.9	21.4	21.7
Ireland	19.0	20.8	21.0	21.6	21.0	23.0	22.0	20.9	22.7	22.8
Poland	18.0†	18.2†	19.9†	20.5†	21.2	24.1	22.0	25.4	24.4	23.6
Spain	16.2‡	16.6‡	15.7‡	16.2‡	17.1‡	17.5‡	27.5	26.8	26.3	24.9
France	25.0	25.1	25.7	25.9	24.9	25.6	25.6	24.7	25.3	25.1
Romania	na	26.5	25.9	26.8	26.6	28.0	24.4	24.5	25.0	25.8
Cyprus	26.3	26.9	25.1	23.9	22.2	26.6	28.4	28.9	28.0	30.1
Greece	35.6	33.4	29.9	29.8	31.0	33.2	33.1	34.2	34.0	34.1

Source: ESAC-Net, ECDC[31]

Note: *, EU/EEA refers to the EU/EEA population-weighted mean consumption based on reported or imputed data from 30 EU/EEA countries; †, Community data only (data from the hospital sector were not reported); ‡, Spain reported reimbursement data for 2011-2015 and changed to sales data in 2016; na, not available.

1.1.3. Antibiotic consumption and Covid-19

Important changes in antibiotics prescription have been observed within the COVID-19 pandemic. Data from the ECDC show a decrease in the total antibiotic consumption in humans between 2019 and 2020 in most EU/EEA countries.[33] This trend was mostly observed in primary care. Among COVID-19 patients, a recent meta-analysis revealed high antimicrobial consumption, at 68%.[34] A subgroup analysis found lower consumption in high-income countries compared with lower and middle-income countries (58% vs 89%). Further research is needed to understand the reasons for variation of antibiotic consumption within the pandemic and the need to address inappropriate antibiotic prescription with antimicrobial stewardship.

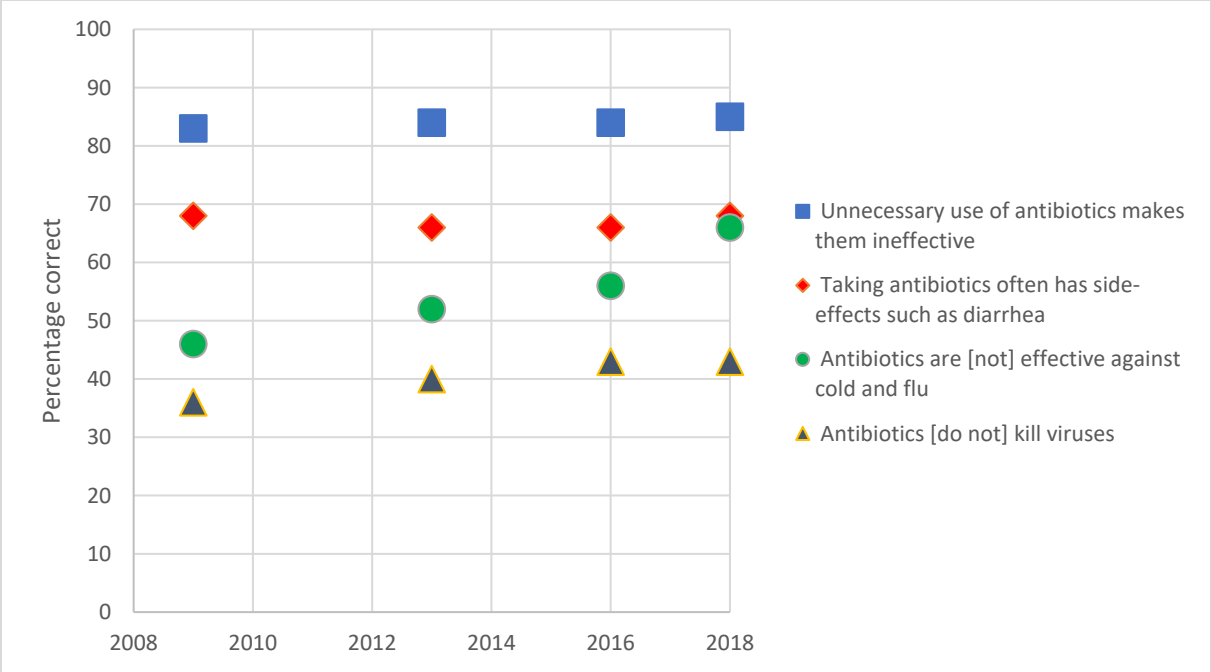
1.1.4. Knowledge, attitudes, and beliefs about antibiotics in Europe

The European Commission has undertaken a series of surveys to assess knowledge, attitudes, and beliefs concerning antibiotics in Europe. These were conducted in 2009, 2013, 2016, and in 2018.[35] In the 2018 survey, 32% of respondents reported having taken antibiotics orally in the preceding 12 months, a small decrease from 34% in 2016. The highest percentage was in Italy, at 47%, while the lowest were in Sweden (20%) and the Netherlands (21%). These figures decreased in most member states, with the largest decreased being observed in Romania (-10 percentage points), followed by Luxembourg, Greece, and Malta. The largest increase was in Denmark (+5 percentage points).

The vast majority of respondents had received their last course of antibiotics from a healthcare professional (93%), either based on a prescription dispensed at a pharmacy (72%) or directly from a medical practitioner (21%), while 7% of antibiotic courses were obtained without a prescription, a figure that was unchanged since 2016.

Respondents were asked questions to test their knowledge about antibiotics. Only 25% got all four answers right, although there was a very small increase in knowledge since 2016 (0.1 on a scale of 1-4). The highest levels of knowledge were in Finland and Sweden, and the lowest in Latvia and Romania. Only less than half (43%) of respondents knew that antibiotics were ineffective against viruses. The ways in which these figures have changed since 2009 are shown in **Figure 5**.

Figure 5 Knowledge about antibiotics in the EU, 2009-2018



Source: Eurobarometer[35]

A third (33%) of respondents recalled receiving information in the previous 12 months about not taking antibiotics unnecessarily. This was unchanged since 2016. The figure was the highest in Finland (59%), which was the only member state where most of the population had received such advice, and the lowest in Romania (14%).

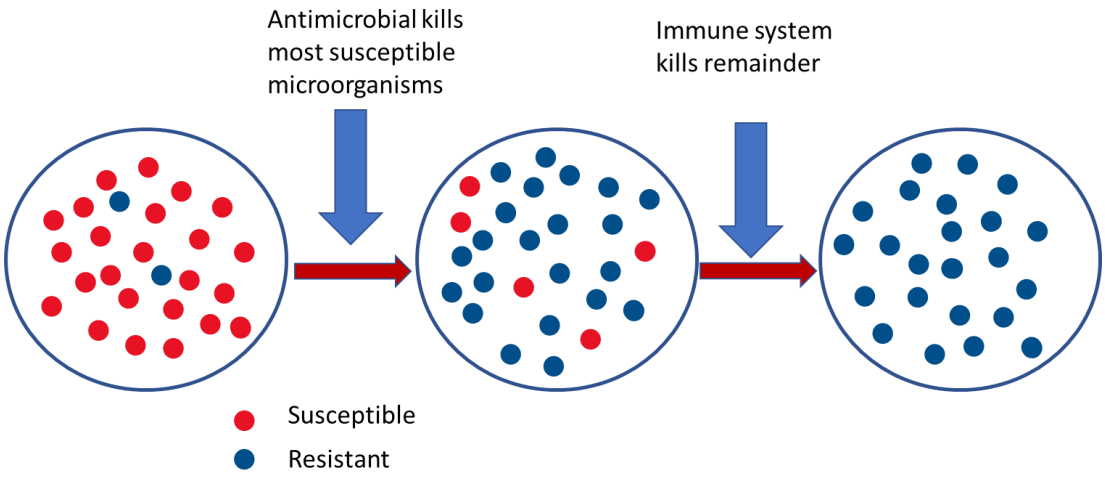
1.2. What contributes to the spread of AMR? A One Health approach (within and beyond health systems) - the role of humans, animals, and the environment

1.2.1. The spread of AMR and One Health approach

In developing our approach to AMR, we conceive the problem as a consequence of evolution of bacteria. AMR arises mainly because of random genetic mutation in a microorganism (for the present purposes we note, but set to one side, the transmission of resistance between microorganisms via plasmids). When a population of microorganisms is exposed to an antimicrobial agent, those susceptible to it will stop reproducing or be killed, as long as concentrations of the antimicrobial are adequate over a long enough period (**Figure 6**). However, it is possible that some, perhaps a few in

several million, by chance possess a genetic mutation that confers resistance to the antimicrobial. Fortunately, when such microorganisms are causing an infection in a human or other animal, the various elements of the immune system will act to kill the by now greatly diminished numbers of microorganisms, including those that are resistant to the antimicrobial in question. However, there are circumstances when this will not happen and the initially very few resistant micro-organisms are able to thrive. Most commonly this is because they are exposed to low levels of the antimicrobial or for inadequate durations to allow the immune system to eliminate the infection. This is most likely to occur with infectious agents that require long, and in some cases lifelong, periods of treatment, such as tuberculosis or HIV, so that treatment involves a combination of agents, each acting in different ways, as the probability that a micro-organism has genes conferring resistance to more than one of them is very small. Other situations include when the infection is overwhelming, the microorganisms are growing in tissues that the antimicrobial cannot reach in adequate amounts (such as areas of necrosis) or, especially when the host is a human, they are immunocompromised. In those circumstances the by now resistant microorganism may survive and given the opportunity, spread to others.

Figure 6 The development of AMR



Source: Authors' compilation

Once a micro-organism has one or more genes conferring resistance, it has an evolutionary advantage in any other situation where it is exposed to the antimicrobial in question. This explains the transmission of antimicrobial-resistant microorganisms between humans, between animals, and between humans and animals and the environment.[36]

Niegowska and Wögerbauer have identified five broad categories within which there are factors that contribute to the spread of AMR:[37]

- **Animal farming**

The use of antibiotics in animals as growth promoters (which is banned in the EU since 2006) or to compensate for poor standards of animal welfare and thus hygiene, inevitably increases the risk of resistance emerging. Vegetables may also be contaminated with antibiotic-resistant bacteria from animal manure used as fertilizer. Antibiotic-resistant bacteria can spread to humans through food and direct contact with animals.

- **Environment**

Wastewater can be contaminated with antibiotics or with resistant bacteria, and in some cases AMR genes transfer. The major sources of wastewater contaminated with antibiotics are from health care facilities, pharmaceutical manufacturing plants, agricultural premises, and aquaculture facilities. The presence of antibiotics at low levels in the environment creates the conditions that encourage resistance to emerge.

- **Community**

Inappropriate use of antimicrobials in the community, for example, when antibacterials are prescribed for viral illnesses or when they are given in sub-therapeutic doses or for inadequate periods, creating the conditions in which the immune system fails to clear them, thus encouraging the development of AMR.

- **Healthcare facilities**

Healthcare facilities are settings that permit or encourage the emergence of AMR in many ways. These include actions that increase the risks of infection (nosocomial infections). While some infections will be inevitable, many represent failures at various points in the patient journey. They include poor hygiene, inadequate pre-operative preparation, medical errors (such as unintended perforation of the gut), poor post-operative rehabilitation (leading to respiratory, urinary, or skin infections), and failure to identify and treat signs of infection early, leading to sepsis.

Health facilities, like any facility in which large numbers of people are brought together, such as prisons, mines, or even cruise ships, can act as institutional amplifiers, where rising levels of infection, including those resistant to antimicrobials, eventually spill into the wider community.[38]

Healthcare-associated infections (HAI) are acquired by patients during their stay in a hospital or another healthcare setting, with different consequences on adverse outcomes, morbidity and length of stays.[39] The most frequent HAI are respiratory tract infections, surgical site infections, urinary tract infections, bloodstream infections and gastro-intestinal infections, with Clostridium difficile infections representing almost half of the gastro-intestinal infections.

- **Travel**

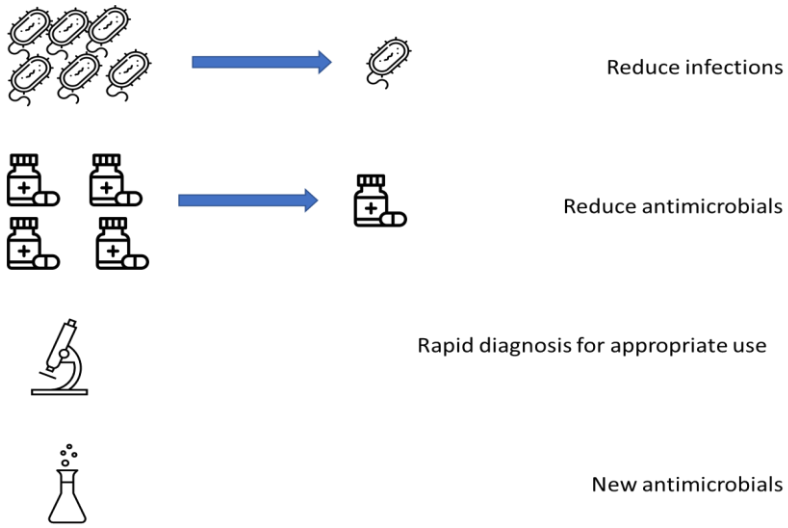
As with any microorganism, human movement facilitates the global spread of resistant bacteria and AMR genes transfer. Travellers that require hospital care while visiting a

country with high prevalence of antimicrobial resistance, within or outside of the EU, and who are subsequently repatriated to their home country, may return being colonised or even infected by multidrug-resistant bacteria. Even without having been in contact with healthcare, people who travel in a country with high prevalence of antimicrobial resistance may return being colonised by multidrug-resistant bacteria. There has been a heightened awareness of this in recent years with respect to the prevalence of infection or colonization with drug-resistant organisms in people who experience short-term international travel, economic migration, and forced displacement from conflict or other disasters.[40] High-income countries are more likely to be recipient nations for AMR originating from middle- and low-income countries. A systematic review of literature until June 2019 showed that the most common origin of travellers with resistant bacteria is Asia, covering 36% of the total isolates. Beta-lactams and quinolones were the most documented drug-resistant organisms, accounting for 35% and 31% of the overall drug resistance, respectively.[41] Health systems should identify recent travellers to ensure that adequate precautions are taken.

1.2.2. Measures to tackle AMR

It follows from the discussion above on the reasons why AMR occurs that there are essentially four ways to reduce it (**Figure 7**).

Figure 7 A taxonomy of approaches



Source: Authors' compilation

Most obviously, anything that reduces the number of infections will reduce both the number of resistant infections and the risk that infections with micro-organisms initially susceptible to antimicrobials acquire resistance. Given the diverse settings in which infections can arise, the range of measures that can be employed is vast. In agriculture they include improved animal welfare standards, with an emphasis on reducing overcrowding and improving hygiene. In the community, they include ensuring supplies

of clean water and, as has become increasingly understood during the pandemic, clean air, with measures such as improved ventilation and filtration to reduce spread of airborne pathogens. It should be recalled that infections often exhibit a steep social gradient and many are, in effect, diseases of poverty. In health facilities, they include measures that span the entire patient journey, from rapid detection of infections on admission, pre-operative assessment, skilled surgical technique, rapid identification of complications, including early signs of sepsis, and effective rehabilitation, all underpinned by high levels of hygiene, surveillance, and infection control. Finally, as the experience with SARS-CoV-2 has shown, advances in vaccine development, in particular those using mRNA, offer great potential for reducing the burden of infection, just as earlier vaccines have done.

Reducing the quantity of antimicrobials used can be achieved by limiting their use to situations where they are necessary. Examples include bans on their use as growth promoters in agriculture or in aquaculture. It can also be achieved by reducing their levels in the environment, for example by controls at pharmaceutical manufacturing plants or health facilities.[42]

It is important to ensure that when they are used, antimicrobials are used appropriately. This requires stewardship, medicines management and prescribing policies. It also requires rapid and accurate diagnosis of infections, rapidly differentiating bacterial from viral infections and ensuring that individuals are not treated with an antimicrobial to which their infection is already partially resistant and thus, likely to amplify the existing level of resistance. This will also reduce the amount of antibacterial used. It is equally important that the antibiotic (as much as possible) only works against the causative bacteria and not against another bacteria (narrow spectrum).

As noted above, there is a particular risk with infections that persists for long periods, such as tuberculosis, where the emergence of resistance is reduced by use of combination therapy. It also involves ensuring that treatment is continued long enough for the immune system to eliminate the infection, with continued monitoring as appropriate to detect early signs of resistance emerging. For acute infections, it is important to ensure a high enough dose (as underdosing can lead to resistance) and that the duration of the treatment is as short as possible.[43]

The discovery and development of new antimicrobials should receive immediate attention. Ideally new antimicrobials should act in different ways from existing ones, and alternatives in which there is less likelihood of pre-existing resistance. For completeness, it is also necessary to mention alternative approaches, such as the use of phages, viruses that attack bacteria, as potential solutions in the fight against AMR.

Measures to reduce the amount of infection and of antimicrobials used, and to improve appropriate use of antimicrobials, can only be implemented if the adequate therapeutic,

diagnostic and preventative medical countermeasures are developed and accessible. Thus, measures promoting the research, innovation, and development, addressing supply chain vulnerabilities, and ensuring access are required for old and new antimicrobials, rapid diagnostic devices and vaccines against resistant pathogens.

Tackling AMR will require all these measures. This will require a comprehensive approach, in which the different elements are closely aligned. Drawing on a recent report prepared for the G7 in 2021,[44] in the next section we identify five broad areas within which to move forward: Policy and strategic planning, Medicines management and prescribing systems, Antimicrobial stewardship (AMS) and multimodal strategies, Research, innovation and technological approaches, and Cooperation to develop new antimicrobials.

1.2.3. Understanding context, culture, and behaviours

Reducing the burden of AMR is not simply a technical matter. The decisions that give rise to it are influenced by the social and economic contexts in which they are made. There are often powerful incentives to make decisions that increase the risk of AMR, for example, financial pressures to prescribe certain medications or fear of failing to treat what might turn out to be a serious bacterial infection. Decisions are also made within professional hierarchies, which may reduce opportunities for evaluation of all the necessary evidence or perpetuate inappropriate behaviours.[45] This topic will also be considered later in this Opinion.

Policy and strategic planning

A sustained reduction in the burden of AMR will only be achieved if it is adopted as a priority at all levels, within countries, regional groupings such as the European Union, and globally. A majority of WHO member states have adopted National Action Plans to reduce AMR. The WHO has identified four objectives that these plans should contain. First, they should promote improved awareness and understanding of AMR, based on effective communication, education, and training. Second, they should strengthen knowledge and be evidence-based through surveillance and research. Third, they should reduce the incidence of infection through effective sanitation, hygiene, and infection prevention. Fourth, they should include measures to optimise antimicrobials in human and animal health. In practice, however, these plans vary in their quality, comprehensiveness, and implementation. Previous analyses suggest that few include a strategic management framework that enables agile responses to emerging threats. In particular, there is often a lack of the intersectoral collaboration that is needed linking health, agriculture, and the food industry.[42] Integration of public health into primary and community health care is also important. Consequently, this Opinion will review the extent to which member states have adopted and implemented appropriate plans and have put in place the means to implement them.

Medicines management and prescribing systems

Medicines management requires that the right antimicrobials, of high quality, are available in sufficient quantity when required. However, in practice, there are many reasons why this does not happen. They include problems of procurement and distribution, including substandard and counterfeit medicines,[46] and inadequate access and affordability by those who need them. Even if they are available, they may not be used appropriately. They may be prescribed inappropriately for patients with infections or without infection that will not benefit from them, or courses of treatment may be terminated early. In circumstances where there is already widespread resistance, the careless use of antimicrobials of last resort can encourage the emergence of resistance to them. Consequently, this Opinion will consider how appropriate antimicrobials can be made available where they are needed and how their inappropriate use can be reduced.

Antimicrobial stewardship (AMS) and multimodal strategies

AMS is a systematic and coordinated approach to optimising antimicrobial use.[47] Its purpose is to promote the prudent use of antibiotics in order to optimize patient outcomes while at the same time minimizing the probability of adverse effects, including toxicity and the selection of pathogenic organisms, and the emergence and spread of antibiotic resistance.[48] Elements include empirical treatment according to local or national guidelines, de-escalation of treatment, parenteral-to-oral switch, therapeutic drug monitoring, and restricted antimicrobial lists, all of which have been shown to produce benefits in terms of clinical outcome, adverse events, treatment costs, and antibiotic resistance.[49]

Successful AMS programmes are multidisciplinary and aligned with an organisation's governance systems. They comprise a suite of coordinated strategies and interventions to promote the optimal use of antimicrobials, tailored to patients' needs. These can be enabling measures, which facilitate appropriate antibiotic treatment, or restrictive ones, that reduce undesirable antibiotic-related decisions. Both are effective, but enabling interventions tend to achieve greater acceptance and improve the sustainability of restrictive ones.[47] The essential elements of AMS programmes are outlined in **Table 2**.

Table 2. Advantages and disadvantages of antimicrobial stewardship measures

Strategy	Procedure	Personnel	Advantages	Disadvantages
Education/guidelines	Creation of guidelines for antimicrobial use	Antimicrobial committee to create guidelines	May alter behavior patterns	Passive education likely ineffective
	Group or individual education of clinicians by educators	Educators (physicians, pharmacists)	Avoids loss of prescriber autonomy	
Formulary/restriction	Restrict dispensing of targeted antimicrobials to approved indications	Antimicrobial committee to create guidelines	Most direct control over antimicrobial use	Perceived loss of autonomy for prescribers
		Approval personnel	Individual	Need for all-hours

Strategy	Procedure	Personnel	Advantages	Disadvantages
		(physician, infectious diseases fellow, clinical pharmacist)	educational opportunities	consultant availability
Review and feedback	Daily review of targeted antimicrobials for appropriateness	Antimicrobial committee to create guidelines	Avoids loss of autonomy for prescribers	Compliance with recommendations voluntary
	Contact prescribers with recommendations for alternative therapy	Review personnel (usually clinical pharmacist)	Individual educational opportunities	
Computer assistance	Use of information technology to implement previous strategies	Antimicrobial committee to create rules for computer systems	Provides patient-specific data where most likely to impact (point of care)	Significant time and resource investment to implement sophisticated systems
	Expert systems provide patient-specific recommendations at point of care (order entry)	Personnel for approval or review (physicians, pharmacists) Computer programmers	Facilitates other strategies	
Antimicrobial cycling	Scheduled rotation of antimicrobials used in hospital or unit (e.g., intensive care unit)	Antimicrobial committee to create cycling protocol	May reduce resistance by changing selective pressure	Difficult to ensure adherence to cycling protocol
		Personnel to oversee adherence (pharmacist, physicians)		Theoretical concerns about effectiveness

Source: MacDougall and Polk, 2005[50]

Systematic reviews document positive outcomes associated with AMS, including reductions in unnecessary antimicrobial use.[49] [51] AMS systems in hospitals have been linked to significant decreases in antimicrobial consumption and cost, and the benefit is higher in the critical care setting, as well as in infections due to specific antimicrobial-resistant pathogens and the overall hospital length of stay are improved as well.[52]

Given the complex nature of antibiotic use, a combination of different measures, in a multimodal intervention, is likely to be most effective. This was seen in a study in a 938-bed hospital in which four interventions were introduced sequentially and evaluated by a mix of quantitative and qualitative methods.[53] The interventions, in order, were: (1) on-request infectious diseases specialist (IDS) consulting service, (2) participation in intensive care unit meetings, (3) IDS intervention triggered by microbiological laboratory meetings, and (4) IDS intervention triggered by hospital pharmacist alert. The number of IDS interventions doubled after implementation of IDS intervention triggered by hospital pharmacist alert. The complete package was associated with a significant decrease of 14.6% in antibiotic use, with fluoroquinolones demonstrating the most marked impact.

The different elements were seen to impact aspects of antimicrobial use in complementary and cumulative ways.

The role of pharmacists in antimicrobial stewardship and the relationship with antibiotic consumption in hospitals is also important. An observational multicentre study showed the relationship between pharmacists' actions and the better control of antibiotic consumption.[54]

In primary care settings, educational interventions have been found to reduce antibiotic prescriptions and inappropriate treatments for urinary tract infection (UTI) without substantially influencing all-cause hospitalisations and mortality. The primary outcome in a Danish randomised controlled trial (RCT) was the number of antibiotic prescriptions for acute UTI per resident per days at risk, defined as the number of days the resident had been present at the nursing home during the trial period.[55] Furthermore, in the HAPPY AUDIT project in 2008, a multifaceted intervention programme targeting general practitioners (GPs) and patients focused on improving diagnostic procedures in patients with respiratory tract infections (RTIs). After three years, there was still a marked reduction in antibiotic prescribing.[56] Even longer-term effects of educational interventions have been documented in this project. Antibiotic prescribing for lower RTIs remained low 6 years after an intervention, although GPs were less confident withholding antibiotic therapy in patients with low C-Reactive Protein (CRP) levels.[57]

Research, innovation and technological approaches

One of the greatest practical challenges in reducing AMR is to ensure that only patients who need antimicrobials receive them. In some cases, it will be possible to make a clinical diagnosis based on the signs and symptoms. This is common in primary care, where more than 80% of antibiotics are prescribed. However, often it will be necessary to obtain a rapid microbiological diagnosis, for example, to differentiate a viral from a bacterial infection or to ascertain whether the microorganisms involved are sensitive to the antimicrobial being prescribed. The ability to do so has been transformed by the development of a range of point-of-care tests and medical technologies including digital health. Technological advances can also contribute by strengthening surveillance systems, for example by linking data from different laboratories or by environmental sampling, for example, of wastewater. Each of these will be considered in this Opinion.

Cooperation to develop new antimicrobials

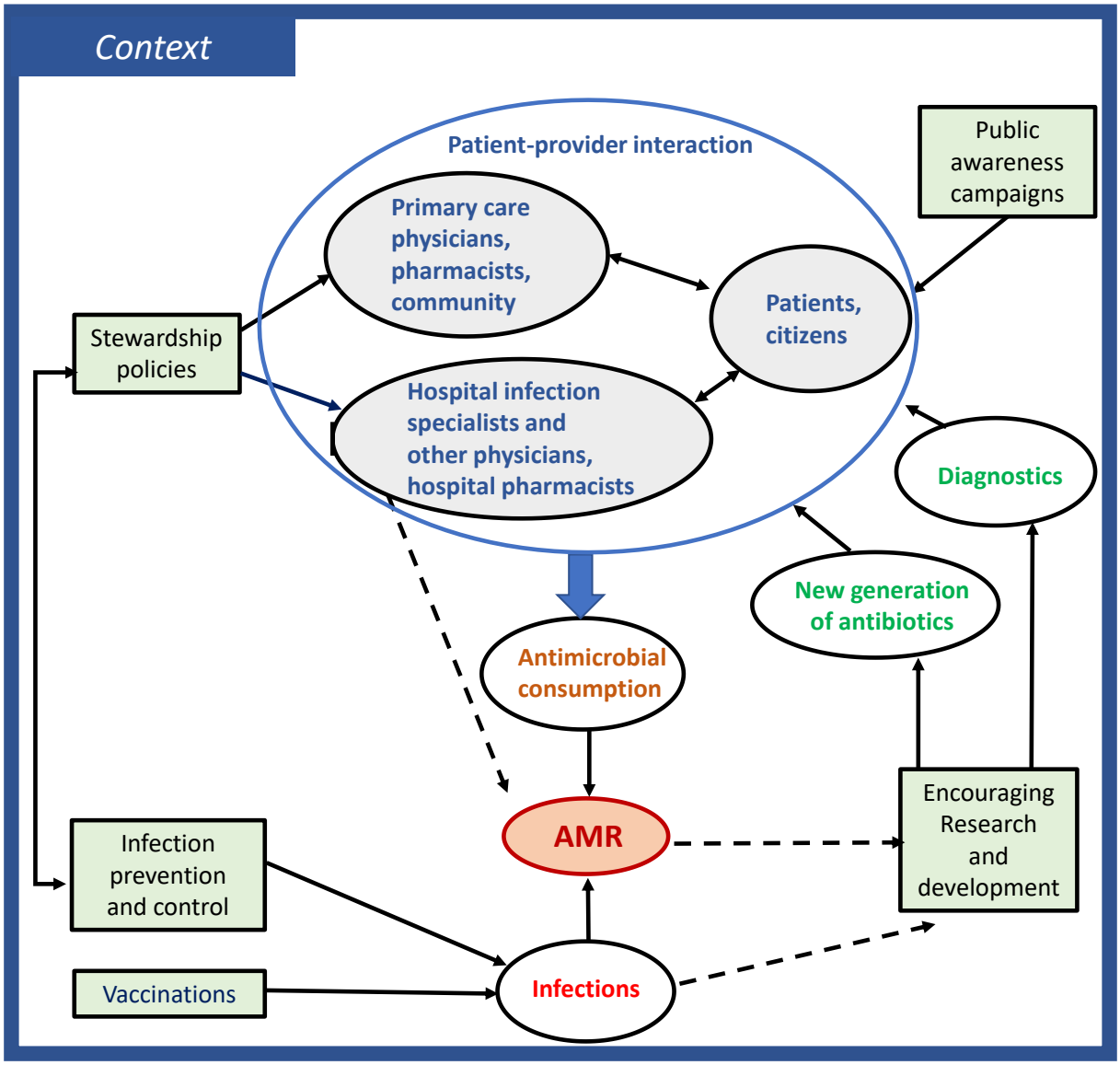
The revitalization of the antimicrobials pipeline is essential.[58] Development and research of new antimicrobials agents needs an evolution of the current mechanisms of financing. Both short-term and long-term solutions to overcome the most urgent limitations in the various sectors of research and funding, aiming to bridge the gap between academic, industrial and political stakeholders, and to unite interdisciplinary expertise in order to efficiently fuel the translational pipeline for the benefit of future generations.[59]

The need for the development of new economic models has been acknowledged in the 2017 EU One Health AMR Action Plan.[1] The need for pull incentives for antimicrobials, specifically, has been acknowledged by the European Commission's 2020 Pharmaceutical Strategy for Europe.[60] There is a need for de-linkage between R&D on the one hand and Production & Sales on the other hand. Inclusion of trans-sectoral partnerships and public-private cooperation is warranted. In France, the National Council of Industry and the government have signed a 'Strategic Contract for the Health Industry and Health Technologies', which describes reciprocal commitments between the government and industry.[61]

1.2.4. A framework for tackling AMR

Figure 8 brings together several of the issues described above taking a health system perspective. The levels of infections and antimicrobial consumption are the two key sources of antimicrobial resistance. Infections can be reduced through prevention and control, and through vaccination and through the use of medical technologies (e.g., diagnostic tests or digital health solutions). Within the health system, antimicrobial consumption is prescribed both within secondary care, where infections are more severe, and within primary care and the community (e.g., by a GP or a pharmacist). Antimicrobial consumption is the outcome of the interaction between the patient and the healthcare provider (e.g., a GP or a hospital specialist). This interaction is influenced by the availability of diagnostic tools and range of available antibiotics (including new generation ones). The patient-provider interaction that ultimately leads to antimicrobial consumption can be influenced by stewardship policies aimed at affecting the behaviour of prescribers, and by public awareness campaigns aimed at affecting patients' attitudes. Policies that stimulate research and development can affect the availability of new antibiotics, which can combat infections more effectively, and the availability of new diagnostic tools that can improve the appropriateness of the prescribed antimicrobials as well as the development of novel antimicrobials treatments and vaccines. At a broader level, it is important to understand the context in which the decisions and actions are made.

Figure 8 Framework for policy interventions at the health system level



Source: Authors' compilation

1.3. What do we know about the determinants of AMR in the health system?

The determinants of AMR in the health system, and of antibiotic use in humans specifically, is particularly complex. Prescribing behaviours play a central role. For example, a comprehensive analysis of the determinants of antibiotic prescribing in human medicine was conducted in Belgium.[62] All primary studies that involved Belgian subjects and were published between January 2000 and April 2018, including Belgian reports and other grey literature were examined. Systematic reviews published between January 2012 and April 2018 and primary studies if they were conducted in countries with similar settings (Western Europe and North America) were also included. The determinants of the choice of the antibiotic molecule were not included, nor specific clinical factors triggering antibiotic prescription (e.g. auscultatory findings for acute cough). The review found that determinants of antibiotic prescribing belonged to various categories: factors related to the prescriber (e.g., socio-demographic factors, attitudes, and beliefs), to the patient (e.g., knowledge and behaviour), to the health care system (e.g., reimbursement system) and to the overall environmental and cultural scheme.

At the prescriber-level, one study of GP prescriptions for sore throat[63] found that prescribing style was an important source of variation in prescription of antibiotics within and across six countries, even after adjusting for patient and GP characteristics.[63] Variation was documented even among GPs from Sweden and Denmark who, as the authors state, work in an environment with a strong political leadership regarding antibiotic stewardship and have guidelines for the management of sore throat patients. This heterogeneity in the prescribing style and variation within GPs has been attributed to the personal psychological/behavioural attitudes towards uncertainty and risk at the GP-level.

The salient beliefs of GPs in Greece towards prescribing have been examined.[64] The expectations of patients and their families were seen as extremely influential during prescribing, while pharmaceutical sales representatives, other GPs and specialists, as well as public health authorities were included among other factors that have an influence on the GPs prescribing. Factors such as the income of the patient, the limited time available and special situations such as prescribing through a third person or prescribing retrospectively, when the patient had already purchased antibiotics over the counter in pharmacies may influence their prescribing decision.[65] Furthermore, a European collaborative study emphasizes the importance of subjective norms in influencing prescribing behaviour and suggests that irrational prescribing behaviours were more apparent in the countries where an integrated primary care system has still not been fully developed and where policies promoting the rational use of medicines are lacking.[66]

The use of antibiotics without prescription is another determinant related to AMR.[67] A reduction of the non-prudent use of antimicrobial drugs without prescription can

contribute to tackling AMR, yet non-prescription antibiotic use is common in all WHO regions according to a recently published systematic review and meta-analysis. The reasons vary among settings.[68] The authors of this study identified positive attitudes to self-medication with antibiotics, relatives having medical backgrounds, older age, living in rural areas, and storing antibiotics at home as risk factors for self-medication with antibiotics. Self-medication is still one of the most common forms of inappropriate use of antibiotics. Within the European Union it was possible to dispense antibiotics for systemic use without a prescription until recently, as in Greece and Bulgaria for example.

Patient demand for antibiotics can be examined via Andersen's expanded behavioural model of health service use. This is an augmentation of Andersen and Newman's behavioural model of health service use and categorizes determinants into psychosocial, enablers and needs. The theoretical basis for the psychosocial categories aligns with the Theory of Planned Behaviour, a classical behaviour model that is widely used in the healthcare research. This model might help explain the overuse of healthcare services that may be associated with an increased demand of antibiotics prescribing. Further research is needed to understand to what extent frequent visitors of primary care services have a higher anticipation of antibiotics prescribing. These models, combined with the components of the Health Belief model (perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action, and self-efficacy), may also provide avenues for research into engaging patients as good stewards of antibiotics.[69]

Although non-prescription use and patient demand are important factors, the general practitioners' perception that the patient wants antibiotics drives prescription behaviour. However, when the patient is asked, he often does not necessarily expect an antibiotic.[70] Therefore, shared decision making processes can reduce antibiotic prescribing in the short-term, as suggested by a 2015 Cochrane Review.[71]

Besides the determinants at individual, physician-patient, and health system levels, national characteristics (e.g., the cultural dimension) and the national environment concerning prescription behaviour are also important determinants.

1.4. What are the innovations and emerging technologies available to improve the fight against AMR, how to support their development?

Several interventions targeting the health system have demonstrated their effectiveness in tackling AMR and emerging technologies can now offer additional perspectives.

Innovative methods and models are required to empower public and professionals to be proactive rather than reactive in a digitalized world. Progress in digital health, mobile technologies and multi-omics technologies are changing the paradigm in healthcare and can contribute to the fight against AMR.

As described in the previous section, uncertainty about the diagnosis of infection can lead to inappropriate antibiotic prescribing, overuse of resources, and disease complications.[72] Emerging technologies can help to reduce this uncertainty.

1.4.1. Strategies to reduce infections – Vaccination and other innovative approaches

Vaccines are used as prophylactics, decreasing the number of infectious disease cases, and thus antibiotic use and the emergence and spread of AMR.[73] *Haemophilus influenzae* type B as well as *Streptococcus pneumoniae* conjugate vaccines have impressive track records in not only preventing life threatening diseases caused by these bacteria, but also reducing antibiotic use and AMR.[74]

Different vaccines are also under development, for example, for *Clostridioides difficile, Escherichia coli, Staphylococcus aureus, Neisseria gonorrhoeae, Pseudomonas aeruginosa* or *Klebsiella pneumoniae*.

Development of next generation vaccines is also part of the strategy against AMR pathogens. This includes reverse vaccinology, enabling the selection of potential vaccine candidates on the basis of the genomic information of a bacterial strain, or structural vaccinology, relying on the combination of structural information with immunological and functional characterization of microbial antigens to structurally design new protective and effective vaccine antigens, or generalized modules for membrane antigens which are outer membrane vesicles generated from Gram-negative bacterial strains that have been genetically modified to enhance release of outer membrane vesicles.

Beside vaccines, there are also several alternative strategies to fight AMR such as the use of therapeutic monoclonal antibodies, microbiota-based interventions, or use of bacteriophages.[75]

1.4.2. Strategies for stewardship and reduction of the use of antimicrobials

Digital education

Common educational methods include one-time seminars and online e-learning modules, but unique strategies such as social media campaigns, educational video games and problem-based learning modules have also been employed. Future studies should focus

on efficacy of educational interventions including providing education to non-prescribing healthcare providers (e.g., nurses, members of the stewardship team) and teaching about disease states beyond upper respiratory tract infections to demonstrate a broader role for education in AMS activities.[76] Educational interventions appear to be an integral component of other interventions of AMS; however, there is a paucity of evidence to support use as a stand-alone intervention outside of regional public health interventions.[76]

A brief digital intervention study in the UK aimed to change patient and public beliefs about antimicrobials and AMR and offers pre-post design evidence in 100 online survey participants.[77] Participants were presented with a hypothetical situation of cold and flu symptoms, then exposed to the intervention. The online intervention comprised: 1) a profiling tool identifying individual beliefs (antibiotic necessity, concerns, and knowledge) driving inappropriate antibiotic demand; 2) messages designed to change beliefs and knowledge (i.e. reduce antibiotic necessity, and increase antibiotic concerns and knowledge), and 3) an algorithm linking specific messages to specific beliefs and knowledge. A significant change in beliefs relating to inappropriate demand was observed after the intervention, with a reduction in beliefs about antibiotic necessity, an increase in antibiotic concerns, and increases in antibiotic and AMR knowledge.

Some educational interventions (i.e., eHealthResp online course for pharmacists and physicians) have been through a process of content validation, although no effectiveness data is available.[78]

Research in behavioural sciences, which explore influences on behaviour and develop and evaluate behavioural interventions, is also important to tackle AMR and improve AMS programs.[79] Focus can be put on ensuring a thorough understanding of behaviours and determinants and intervention functions that contribute to the identified AMS/AMR-related problem before trying to change them.

Innovative reimbursement strategies

Friedrich has argued that existing health financing models often create disincentives for measures that could improve antimicrobial stewardship, in particular by failing to reward prevention.[80] A Belgian study quantified the difference in fluoroquinolone use after a change of the nationwide criteria for the reimbursement of fluoroquinolones on 1 May 2018. Fluoroquinolone use dropped significantly immediately after the change in reimbursement criteria, from 2.21 expressed in Defined Daily Dose per 1000 inhabitants per day (DID) (95% CI: 2.03–2.38) to 0.52 DID (95% CI: 0.48–0.56) and from 9.14% (95% CI: 8.75%–9.56%) to 6.52% (95% CI: 6.04%–7.04%). The observed decrease in fluoroquinolone use persisted over time and the change in reimbursement criteria helped to lower fluoroquinolone use in Belgium.[81]

In Belgium, an assessment was made in 2019 by the National Institute for Health and Disability Insurance (NIHDI), comparing antibiotic prescription indicators in fee-for-

service practices without a patient list with the same indicators in capitated practices with empanelment of patients. **Table 3** shows the results of this comparison, which suggest that capitation and empanelment was associated with lower antibiotic prescription than fee for service.

Table 3 Comparison of antibiotic prescriptions in Belgium: fee-for-service versus capitation (primary care) in 2016

Indicator	Fee-for-service No patient list	Capitation Empanelment
P50: Percentage of patients with one or more antibiotic prescriptions	32%	14%
P50: Percentage of 'second line' antibiotic prescriptions (broad-spectrum) (amoxicillin-clavulanic acid, cephalopsporins, quinolones, macrolides)	53%	32%
P50: Percentage of prescriptions of amoxicillin, not combined with clavulanic acid	53%	72%

Source: Leroy et al. 2019 [62]

Approaches to tackling AMR through reimbursement strategies for incentivising innovation in France and Germany are outlined in **Table 4**.[61] France and Germany implemented interventions centred on providing exceptions in cost-containment mechanisms to allow higher prices for certain antibiotics.

Table 4 Summary of novel reimbursement mechanisms relevant to AMR in select European countries

Country	Name	Timeline	Mechanism type	Antimicrobials/ pathogens targeted
France	Exception for antibacterials with ASMR level IV (minor	In effect since 2015	Medicines with' moderate' or higher added therapeutic benefit are guaranteed a price not lower than the lowest price across 4 reference countries. This is extended to antibacterials with 'minor' added therapeutic benefit.	Antibacterials assessed as being ASMR level IV (minor)
	Exemptions in clawback scheme	In effect since 2015	Sales of certain medicines exempted from turnover liable to clawback	Antibacterials and other medicines used in combatting AMR
	Price renegotiation for medicines at risk of shortage	In effect since 2015	Companies may request permission for a price increase from the reimbursement authority, if continued commercialisation would otherwise not be viable	This mechanism has been used for antimicrobials, though details are confidential
Germany	Changes in the Social Code for Statutory Health Insurance covering fixed amounts of medicines	In effect since 2017	*Ad hoc* exception of antimicrobials from internal price reference groups	Decided by reimbursement authority *ad hoc* taking into consideration resistance pattern
	Fair Health Insurance Law	In effect	Automatic exception of	'Reserve'

	(Faire Kassenwettbewerbsgesetz)	since March 2020	'reserve' antibacterials from internal price reference groups, accelerated reimbursement review process following EMA approval	antibacterials* Reserve group' is to be defined by the Robert Koch Institute and the Federal Institute for Drugs and Medical Devices.

Source: Gotham et al., 2021[61]

Public awareness campaigns

Provision of knowledge about the appropriate use of antimicrobials has an intuitive attraction but, from a knowledge translation perspective, there are many reasons for caution. Public awareness campaigns seek to address a knowledge deficit that, when corrected, may help to decrease antibiotic consumption in the general population and help to tackle AMR. Since 2008, the ECDC has coordinated European Antibiotic Awareness Day (EAAD), which provides support to national campaigns to raise awareness of prudent use of antibiotics and of AMR in the EU/EEA. Although numerous additional factors contribute to the inappropriate use of antibiotics, there is some evidence that public awareness campaigns can have a positive impact. A 2012 meta-analysis concluded that mass media campaigns do have a small but statistically significant effect on the general population's attitudes to and knowledge of inappropriate antimicrobial use.[82] A subsequent review of studies from Italy, the United Kingdom and the United States concluded that mass media campaigns could decrease antibiotic consumption by 6.5%.[83] Most recently, a study of two decades of experience with the campaigns used by the Belgian Antibiotic Policy Coordination Committee concluded that their mass media campaigns had achieved significant increases in antibiotic awareness.[84]

1.4.3. Strategies for rapid diagnosis based on emerging technologies and digital interventions

Since AMR is a huge problem on a global level, it requires innovative methods and models to empower public and professionals to be proactive rather than reactive in a digitalized world. Progress in digital health, mobile technologies and multi-omics technologies are changing the paradigm in healthcare and confer expected benefits in the fight against AMR. As described in the previous section, uncertainty about the diagnosis of infection can lead to inappropriate antibiotic prescribing, overuse of resources, and disease complications.[72] Emerging technologies may help to reduce this uncertainty.

Telemedicine

Telemedicine and telehealth can help to support AMS activities across a range of clinical areas to connect healthcare providers with infectious disease specialists, clinical microbiologists, and/or pharmacists. These activities can occur at the level of pre-authorizations, post-prescription reviews, and/or education. For example, low-cost videoconferencing systems can be employed to conduct individual patient reviews, or

virtual AMS ward rounds can be conducted with the remote team. Models for providing AMS via telehealth include regular weekly AMS case conferences and virtual AMS bedside rounds, and prescriptions being reviewed remotely before being dispensed.[64] A review of the available literature suggests remote AMS programmes conducted via communication technologies connecting healthcare providers with specialists (e.g., phone calls, video conferencing, email, electronic medical record documentation, or other methods of remote communication), can decrease antimicrobial consumption, especially in small rural or community hospitals.[85]

A study conducted in a high-specialized paediatric cardiac hospital evaluated the impact of remote infectious disease consultancy program via telemedicine.[86] After the implementation of the telemedicine service, the authors showed a trend in the reduction of nosocomial infectious disease rate, with a reduction in the overall antibiotic cost and in the average antibiotics packages used per admission. They also observed a significant reduction in isolates of multi-drug resistant bacteria.

Electronic clinical decision support systems (eCDSS)

eCDSSs can assist clinicians to make more accurate and timely diagnosis, and aid in the decision to prescribe antimicrobials for a patient. Key infectious diseases bodies support the use of eCDSSs as potentially useful tools in AMS programs, especially for providing access to data that can support quality improvement initiatives. Many studies report cost avoidance or cost minimisation because of implementing an eCDSS, although rigorous cost-effectiveness or cost–benefit analyses are lacking. Reported savings include reduction in antimicrobial expenditure, reduction in length of stay, and reduction in hospitalisation costs.[64]

eCDSSs that effectively support the AMS clinical team incorporate alerts, prompts and restrictions, and allow integration with pharmacy and microbiology laboratory systems. The most common uses of IT systems to provide decision support for AMS include: 1) Passive decision support through electronic access to guidelines and mobile applications; 2) Electronic antimicrobial approval systems; 3) Electronic infection prevention surveillance systems; 4) Electronic prescribing (e-prescribing) and electronic medication management; and 5) Advanced decision support.

Biomarker-based antibiotic stewardship

The clinical implications of AMR include treatment failure of antibiotic therapy due to insufficient efficacy or occurrence of toxicity. Current solutions involve therapeutic drug monitoring to optimize antibiotic exposure. Biomarker-based strategies have been proposed as a powerful tool to further quantify and monitor antibiotic treatment response and reduce variation in treatment response between patients.[87]

Proposed suitable biomarkers include C-reactive protein (CRP; a hepatic acute phase protein playing a crucial role in the innate host defence by activating the complement system and promoting phagocytosis of pathogens) and Interleukin-6 (IL-6; a cytokine

produced by immune cells and stromal cells, involved in inflammation, and plays a pivotal role in orchestrating the immune response to infection). Procalcitonin (PCT) is particularly promising.[88]

PCT is a precursor to the hormone calcitonin, and, under normal conditions, produced only intracellularly by parafollicular cells in thyroidal tissues. However, during microbial infections and severe systemic inflammation, PCT production is induced throughout the body where it is thought to be associated with immune modulatory properties. PCT-guided antibiotic treatment termination can lead to a significant reduction of antibiotic exposure in sepsis and respiratory tract infections. Recent data showed also that PCT was able to distinguish those COVID-19 patients with secondary bacterial infection.[89] PCT is also reported to have economic value and cost saving benefits.[90]

Furthermore, a combination of biomarkers is another strategy with potential added value where the accuracy of diagnosis was improved in conditions, like neonatal sepsis for example.[91] **Figure 9** illustrates the use of biomarker informed treatment individualization strategies.

Figure 9 Overview of the use of biomarker-informed treatment individualization strategies

Phase	**1** **Start of treatment**	**2** **During treatment**	**3** **End of treatment**
Action	Select drug and dose	Adjust drug and dose	De-escalation
Tools	Pathogen identification Pharmacokinetic biomarkers Susceptibility testing Pharmacogenomics	Efficacy biomarkers Toxicity biomarkers Therapeutic drug monitoring Pharmacokinetic related biomarkers	Clinical symptoms Efficacy biomarkers Microbial cultures

Source: Aulin et al. 2021[87]

Current empirical antibiotic treatments are associated with significant risk of toxicity, treatment failure, and antibiotic resistance development. These risks could be reduced by optimizing antibiotic treatments at an individual level. Specifically, treatment individualization strategies informed by biomarkers could play an important part. Such biomarkers can inform on pharmacokinetics, efficacy, and toxicity, and guide the treatment throughout all phases of infection.[87]

Testing could also be relevant to confirm suspected β-lactam allergy. Patients with supposed allergy to β-lactams can undergo diagnosis with skin testing and drug challenge at the end.[92] This strategy might optimize the access to β-lactams and prevent

the prescription of other antibiotics. More evidence and Health Technology Assessment based approaches will be required to confirm the effectiveness of this strategy.

Point-of-care testing (POCT)

Point-of-care testing (POCT) allows the analysis to be performed close to or near the patient. It is seen as especially promising as a means of enhancing antibiotic stewardship. Measurement of CRP blood concentrations by POCT enables clinicians to differentiate bacterial infections from other inflammatory disorders and thus identify patients who are most likely to benefit from antibiotics. The robustness and accuracy of CRP-POCT compared with laboratory testing have been demonstrated by diagnostic studies. CRP-POCT has also been integrated into some clinical guidelines as part of the assessment for respiratory tract infections (RTIs) to reduce diagnostic uncertainty and to aid prescribing decisions. According to a 2020 meta-analysis, CRP-POCT significantly reduced immediate antibiotic prescribing at the index consultation compared with usual care (RR 0.79, 95% CI 0.70-0.90) but not during 28-day (*n*=7) follow-up. The immediate effect was sustained at 12 months (*n*=1). In children, CRP-POCT reduced antibiotic prescribing when CRP (cut-off) guidance was provided (*n*=2). Meta-analyses showed significantly higher rates of re-consultation within 30 days (*n*=8, 1 significant). Clinical recovery, resolution of symptoms, and hospital admissions were not significantly different between CRP-POCT and usual care. CRP-POCT can reduce immediate antibiotic prescribing for RTIs in primary care [number needed to (NNT) for benefit=8] at the expense of increased re-consultations (NNT for harm=27).[93]

Several studies published after the meta-analysis add to the evidence of effectiveness. For instance, one study randomized general practitioners to either antibiotics guided by sequential procalcitonin (PCT) and lung ultrasonography point-of-care tests (UltraPro; n=152), PCT-guided antibiotics (n=195), or usual care (n=122). Compared with usual care, point-of-care PCT led to a 26% absolute reduction in the probability of 28 day antibiotic prescription without affecting patients' safety.[94] In a nursing home study, CRP-POCT for suspected lower RTI safely reduced antibiotic prescribing compared with usual care in residents.[95]

Two additional studies highlight the importance of availability of CRP-POCTs. In one study, GPs were exposed to a multifaceted intervention and given access to a CRP rapid test, while in the partial intervention group, GPs were only exposed to the multifaceted intervention. Antibiotic overprescribing was only reduced when CRP rapid test was available.[96] These data have been supported by a recently published prospective audit study that was carried out in 18 countries.[97] Although a high confidence in decisions about antibiotic prescribing was reported, there was also considerable variation in GPs antibiotic prescribing behaviour for RTIs. Furthermore, for antibiotics and overall, there was more prescribing than is considered appropriate. POCTs testing have the potential to enhance the quality of antibiotic prescribing decisions to the extent to which it can safely

reverse decisions confidently made on clinical grounds alone to prescribe antibiotics. Importantly, in Section 2 of this Opinion, the conditions and strategies associated with effective implementation of POCTs are described.

Omics technologies to detect antibiotic resistance genes in the environment

Recent advances in "omics" technologies (genomics, transcriptomics, proteomics, and metabolomics) are attributed to innovative breakthroughs in genome sequencing, bioinformatics, and analytic tools such as liquid and gas chromatography and mass spectrometry, along with high-throughput technologies. Omics technologies have provided crucial insights into processes related to bacterial physiology, virulence, stress, and the mechanisms of action of antimicrobial compounds. The use of these tools provides deeper and more robust data and has greater potential to reveal new therapeutic targets than conventional assays. These approaches have the potential to provide new insights into our comprehension of antimicrobial resistance/susceptibility, creating new perspectives for the struggle against bacteria, and leading to the development of novel products in the future.[98]

Multi-omics approaches for screening

Whole-genome sequencing for antibiotic susceptibility testing (WGS-AST) is widely used in clinical microbiology to predict the AMR phenotype. To release the limitations of the genomic information and improve the WGS-AST prediction, an integrated multi-omics approach has been suggested. Preliminary evaluation results show that the integrated multi-omics approach is able to visually reveal AMR phenotype of the gut microbiota via antibacterial spectrum, and achieves relatively better performance than the conventional Whole Genome Sequencing for bacterial antimicrobial susceptibility testing.[99] Multi-omics analysis on antimicrobial resistance has also been successfully used to collect extensive standardized freshwater dataset from hundreds of European lakes, which can be used as a comprehensive resistome, a collection of all the antibiotic resistant genes and their precursors in pathogenic and non-pathogenic bacteria, dataset to facilitate and monitor changes in the development of AMR.[100]

Metagenomics and network medicine

Metagenomic next-generation sequencing (mNGS) is a more rapid and agnostic diagnostic approach for microbiome and resistome investigations. So far, mNGS have proven to detect multidrug-resistant organisms (MDROs) from rectal swabs in concordance with standard microbiology results.[101] Metagenomic techniques, using short-read next-generation sequencing data, benefit from the ability to quantify thousands of especially transmissible resistance genes in a single sample. Moreover, it can provide additional information about the presence of bacterial species, pathogens, and virulence genes and the data can be re-analysed if novel genes of interest are identified.

Metagenomic analysis has been used to analyse untreated sewage to characterize the bacterial resistome from 79 sites in 60 countries.[102] From a surveillance point of view,

urban sewage is attractive because it provides sampling material from a large and mostly healthy population, which otherwise would not be feasible to monitor.

Clinical metagenomics (CMg) has the potential to be translated from a research tool into routine service to improve antimicrobial treatment and infection control decisions. CMg testing provides accurate pathogen detection and antibiotic resistance prediction in a same-day laboratory workflow, with assembled genomes available the next day for genomic surveillance. The provision of this technology in a service setting could fundamentally change the multi-disciplinary team approach to managing intensive care unit (ICU) infections, improving the initial targeted treatment and rapidly detecting unsuspected outbreaks of AMR.[103]

Network medicine is a rapidly growing discipline that considers diseases as the consequences of perturbed interactions between multiple interconnected biological components. This powerful integrative approach has enabled several important discoveries in complex disease mechanisms. The combination of multi-omics approaches, deeply characterizing the clinical phenotype and machine learning through network medicine offer new perspectives to prevent AMR and to enhance the understanding of complex health interactions.

1.4.4. Strategies to develop new antimicrobials

CRISPR-Cas9 antimicrobials

The clustered regularly interspaced short palindromic repeats (CRISPR)-associated (CRISPR-Cas) system, as a bacterial adaptive immune system, is recognized as one of the new strategies for controlling antibiotic-resistant strains. The programmable Cas nuclease of this system used against bacterial genomic sequences could be lethal or could help reduce resistance of bacteria to antibiotics.[104]

CRISPR-Cas9 is an "Ribonucleic acid (RNA)-guided-Deoxyribonucleic acid (DNA) cutter". Upon bacteriophage infection inside the bacteria, the Cas barcodes small phage genome sequences into the genome of bacteria to counterattack using CRISPR-Cas9 to cleave foreign genetic material. One of the most dynamic and specific key features of this system is 'sequence-specific targeting', the ability to distinguish between commensal and pathogenic bacterial species. Guide CRISPR-RNA can be constructed to target only chromosomal and virulence genes that are highly specific to pathogens, therefore, enabling this system to be reused against the bacteria rather defending against invaders. For instance, the newly developed CRISPR/Cas9 "pro-active" genetic system (Pro-AG) could potentially be used to eliminate of bacterial virulence factors carried on virulence plasmids and resistance determinants in commensal bacteria. Since Cas9 has nuclease activity, it can be programmed with a particular target sequence, enhancing the cytotoxicity of resistant cells. Therefore, a CRISPR-guide RNA can be designed specifically

to target resistance or virulence genes, it will induce a break inside the double-stranded DNA of resistant bacteria, reverting them into the antibiotic sensitive ones.[105]

However, the utilization of CRISPR-Cas to eliminate AMR genes has only been assessed in near-clonal bacterial populations and not in a complex microbial community. Using such an approach in natural environments, where bacteria are typically lodged in a microbial community, is challenging.

Moreover, despite increasing studies have shown the use of phage-based delivery of CRISPR-Cas antimicrobials to remove AMR plasmids or kill AMR pathogens, there are still some limitations in the therapeutic applications of CRISPR-Cas antimicrobials in terms of this phage-based delivery method. In addition to establish delivery vehicles for CRISPR-Cas antimicrobials, how to transport them to target intracellular pathogens is another major challenge.[106]

Although studies have shown the strong potency in bacterial killing using the CRISPR-Cas antimicrobials, there are still colonies that survived by escaping genome targeting. Several factors mainly contribute to the emerged resistance against CRISPR-Cas antimicrobials in the escaped colonies, such as the spontaneous mutations in the Cas genes or the target sequences, spacer excision owing to the homologous recombination between the repeats, presence of the anti-CRISPR Acrosin (Acr) genes in the target host genomes, and repressed expression/activity of Cas proteins.[106]

Machine learning

The recent advances made in data science, artificial intelligence (AI) and machine learning algorithms offer novel opportunities for the surveillance of antibiotic resistomes, as well as experimental formulation of combinatorial drugs.

The following are some potential applications of machine learning in the fight against AMR:

Decelerating the spread of antibiotic resistant genes, surveillance of the resistome is of utmost importance. The integrative applications of whole-genome sequencing and metagenomics together with machine learning models serve as means for state-of-the-art surveillance of the antibiotic resistome.[107]

AI can be used for monitoring and quick alert. It can be applied to generate standardized data that can be compared between nations, track the emergence and spread of AMR genes and assist in the allocation of required resources.

Machine learning can facilitate future identification of new antibiotics and drug repurposing. The general power of neural networks for detecting new antimicrobial candidates has already been demonstrated.[108] By using a computational model that screens hundreds of millions of chemical compounds in a few days, potential antibiotics could be proposed rapidly.

Machine learning can be included in the process of antibacterial drug discovery and development.

AI can be used for more efficient distribution of tasks and actions to tackle AMR across the health systems. Tasks can be shifted from health workers to patients and their care givers, to machines, and to other health workers. Where these shifts have been evaluated, they often, but not always, are associated with outcomes that are as good as, or even better than, the status quo.[109]

Machine learning can enhance integration and optimization of primary care and hospital resources.

If CRISPR-Cas9 antimicrobials and machine learning could prove beneficial, new product categories or development methods alone will not help tackle AMR unless the market failure underlying the antimicrobial space is fixed first, and new technologies can effectively reach the patients.

Table 5 provides a summary of the innovations and new technologies being developed and deployed to tackle AMR, along with an assessment of associated opportunities and challenges, and effectiveness and cost-effectiveness data when available.

Table 5 Innovations and new technologies being developed and deployed to tackle AMR

Innovations and New Technologies	Opportunities	Challenges	Effectiveness	Cost-effectiveness
Strategies to reduce infections				
Vaccine and alternative approaches	Treatment, prevention and control	Broader adoption by the community	Reduction of infections and AMR	Savings on healthcare expenses
Strategies to reduce use of antimicrobials				
Education of prescribers	Optimise antimicrobial use	Multidisciplinary actions and coordination	Reductions in unnecessary antimicrobial consumption	Reduction in costs
Innovative reimbursement strategies	Control of antimicrobial prescription			Savings on antimicrobials expenditures
Public awareness campaigns	Effective implementation of critical interventions	Integral component of other AMS interventions	Scarce evidence as a stand-alone intervention	Lower cost compared to non-digital
Strategies for rapid diagnosis based on emerging technologies and digital interventions				
Telemedicine	Support AMS activities	Deployment	Decrease antimicrobial consumption in small rural or community hospitals	Low-cost videoconferencing and education programs
Electronic clinical decision support systems	Provide access to data that support quality improvement	Important to incorporate alerts, prompts and restrictions, and allow integration with pharmacy and microbiology laboratory systems	Support AMS	Savings on antimicrobial related expenditures
Biomarkers based antibiotic stewardship	Optimize antibiotic treatments at an individual level Reduction of diagnostic uncertainty	Need to integrate multiple datasets	Reduction of treatment toxicity, treatment failure and AMR	Reduction in costs and improved clinical outcomes
Point-of-care testing	Discern bacterial	Setting legal	Reduction in	Expected higher cost

Innovations and New Technologies	Opportunities	Challenges	Effectiveness	Cost-effectiveness
(POCT)	infections from other inflammatory disorders Rapid diagnosis Reduce clinical uncertainty	framework in primary care Cost / reimbursement	antibiotic prescribing	than central clinical laboratories but more targeted test prescription and sustainable approach
Omics technologies to detect antibiotic resistance genes in the environment	Potential to reveal new therapeutic targets Improved surveillance	Complexity, and wide dynamic range of the samples	Improved prevention, surveillance and control	High operating costs
Multi-omics approaches for screening	Predict AMR phenotype	Data management and integration	Better performance than the conventional Whole Genome Sequencing	High operating costs and need of bioinformatic support
Metagenomics / mNGS and network medicine	Improve the initial targeted treatment; AMS	Labor-intensive, highly skilled	mNGS have proven to detect MDRO from rectal swabs in concordance with standard microbiology results	Expensive
Strategies to develop new antimicrobials				
CRISPR-Cas9 antimicrobials	CRISPR-Cas9 can be designed specifically to target AMR	Need to establish delivery vehicles for CRISPR-Cas antimicrobials; how to transport them to target intracellular pathogens; how can the emergence of resistance to CRISPR-Cas be avoided	Use of phage-based delivery of CRISPR-Cas antimicrobials to remove AMR plasmids or kill AMR pathogens	Investment for more research, developments and translation to practices
Machine Learning	Support to clinical decision Surveillance of AMR Identification of novel treatments	Need of structured and interoperable data Security and safety of data exchanges Human warrantee	Identification of new drugs Monitoring of AMR	Improved efficiency and maximize human resources Sustainable

Source: Authors' compilation

2. Policy analysis

2.1. A One Health Approach to tackling AMR

In May 2014, the World Health Assembly issued resolution WHA67.25 to develop a global action plan (WHO GAP) on antimicrobial resistance. The plan was developed by the World Health Organization in collaboration with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (WOAH, founded as OIE). These three organizations are referred to as "the Tripartite" and have since been joined by the United Nations Environment Programme (UNEP) to form the Quadripartite. The Quadripartite coordinates global activities to address health risks at the animal-human-ecosystems, promoting the One Health Approach as the guiding frame for national responses to AMR.

The WHO GAP was endorsed in May 2015 and identifies five strategic objectives:

1. to improve awareness and understanding of AMR through effective communication, education and training;
2. to strengthen knowledge through surveillance and research;
3. to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures and solutions;
4. to optimize the use of antimicrobial agents in human and animal health; and
5. to 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.[110]

For each objective, it detailed specific actions for Member States, its Secretariat, and international and national partners. Countries agreed to develop national action plans on AMR that are consistent with the WHO GAP and to implement relevant policies and plans to prevent, control and monitor AMR. In brief, actions to address awareness include communication programmes, AMR as a core component of professional education, training, and certification, and inclusion of antimicrobial use and resistance in school curricula. Actions to address surveillance include developing a national surveillance system for AMR that includes a national reference centre able to systematically collect, analyse, and report data and at least one reference laboratory capable of susceptibility testing using standardized tests and operating under agreed quality standards to fulfil the core data requirements. In the area of infection prevention and control, recommendations include training and education in hygiene and infection prevention and control component of professional education, training, and certification, developing/strengthening policies and standards while monitoring implementation and adherence, and incorporation of collecting and reporting of data on antimicrobial susceptibility of microorganisms causing health care-associated infections. With respect to optimization of antimicrobial use, actions include developing/implementing enforceable

regulatory frameworks for marketing, distribution, prescriptions, dispensing, and reimbursements, as well as provision of stewardship programs and modification of economic incentives to encourage appropriate use of antimicrobial agents. Lastly, with respect to the economic case, actions include assessing and financing national action plans and participating in research to support the development of new medicines, diagnostic tools, and vaccines.

In 2016, the organizations launched the first Tripartite Annual Country Self-Assessment Survey (TrACSS).[111] National authorities conduct a self-assessment of actions in relevant sectors, identifying progress under a series of topics. Each country is asked to submit one combined official response, validated by all sectors involved, which summarises national progress. The responses are structured according to the first four WHO GAP objectives. Most questions ask for a rating of national capacity and progress on a five-point scale (A to E) which encompass both progress and functionality. They indicate whether policies and plans are in place and how far activities are being implemented. Several questions refer to tools or guidance developed by FAO, WOAH (founded as OIE), or WHO that can help build country capacity in addressing particular areas. The survey is now conducted annually and the resulting data have contributed to the development of a Strategic Framework that addresses identified areas of need and, at the same time, incorporates new questions as guidance evolves.

The Strategic Framework, published in April 2022,[112] documents the goal and two supporting objectives, along with overall impact, longer-term outcomes focusing on countries, and two intermediate outcomes and related functions/outputs at 1) country level and 2) global/regional levels.

The overall goal of the Strategic Framework is to preserve antimicrobial efficacy and ensure sustainable and equitable access to antimicrobials for responsible and prudent use in human, animal, and plant health, contributing to achieving the Sustainable Development Goals (SDGs). The two objectives are:

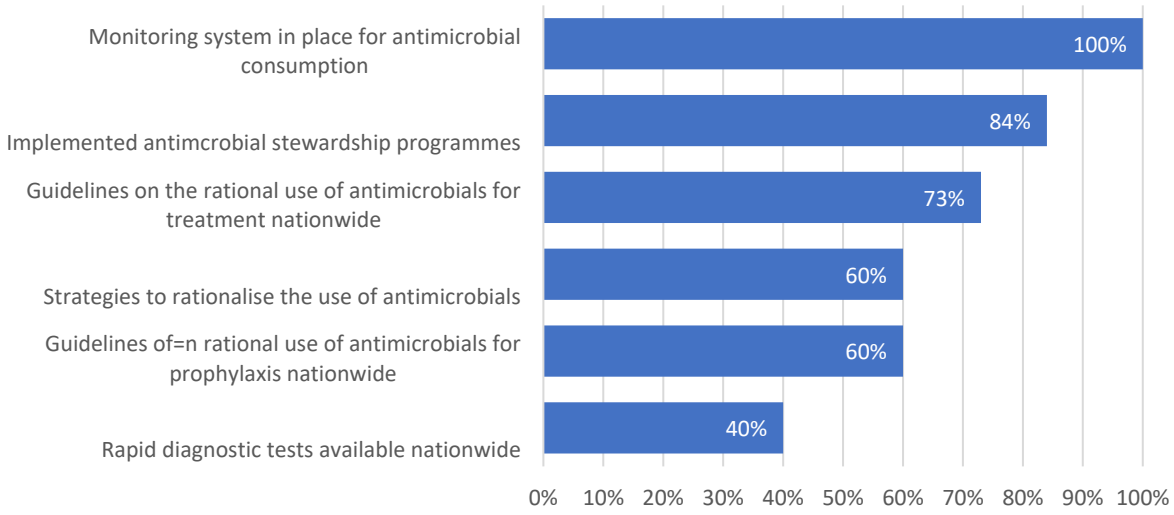
1. to optimize the production and use of antimicrobials along the whole life cycle from research and development to disposal;
2. to decrease the incidence of infection in humans, animals, and plants to reduce the development and spread of AMR.

The annual TrACSS surveys reveal considerable differences in the progress made by countries, and in their capacity, resources and context. For instance, although most countries surveyed have developed a national action plan, few have the necessary approved and budgeted operational plan to implement it. This reflects lack of capacity to coordinate, monitor, and adapt responses to AMR. Less than half of the countries surveyed have nationwide implementation of infection prevention and control in human health facilities aligned with WHO guidelines. Multi-sectoral working groups, which are critical to a successful One Health approach to tackling AMR, are functional in only half of

countries surveyed and only a third balance representation across human, animal, and plant health and the environment.

Specific to health systems, in an examination of 29 OECD countries, the numbers implementing policies to promote the rational use of antimicrobials vary by policy (**Figure 10**). While all 29 reported a monitoring system in place for antimicrobial consumption, only 40% reported rapid diagnostic tests available nationwide.[17]

Figure 10 Proportion of OECD countries implementing specific policies to promote the rational use of antimicrobials



Source: OECD, 2018[17]

2.2. AMR Policy in the European Union

This section provides background information on the EU One Health Action Plan. It offers specifics on certain aspects of the plan but does not (in this section) assess progress made. In 2016, the Council issued a series of conclusions on "next steps under a One Health approach to combat antimicrobial resistance". It called upon member states to develop national action plans based on the One Health approach and in line with the WHO GAP objectives, on the member states and the Commission to work together to develop an Action Plan, and the Commission to take a series of measures to support these developments.[113] The Action Plan was published the following year.[1] The Plan sets out a series of high level objectives, backed up by a list of actions to be taken by the Commission.

The key objectives of the plan are built on three main pillars:

1. Making the EU a best practice region. As the evaluation of the 2011 action plan highlighted, this will require better evidence, better coordination and surveillance, and better control measures. EU action will focus on key areas and help Member States in establishing, implementing and monitoring their own national One

Health action plans on AMR, which they agreed to develop at the 2015 World Health Assembly;

2. Boosting research, development and innovation by closing current knowledge gaps, providing novel solutions and tools to prevent and treat infectious diseases, and improving diagnosis in order to control the spread of AMR;
3. Intensifying EU efforts worldwide to shape the global agenda on AMR and the related risks in an increasingly interconnected world.

While the Action Plan is written for the Commission, most of the commitments it contains are equally relevant for member states (**Table 6**).

Table 6 Recommendations from the EU One Health Action Plan specifically concerning making the EU a best practice region in tackling AMR

Goal	Commission action
Strengthen One Health surveillance and reporting of AMR and antimicrobial use	Review EU implementing legislation on monitoring AMR in zoonotic and commensal bacteria in farm animals and food, to take into account new scientific developments and data collection needs.
	Review EU implementing legislation on reporting communicable diseases in humans to take into account new scientific developments and data collection needs.
	Identify and assess under the Animal Health Law and with the support of the EFSA, resistant bacteria that cause transmissible animal diseases and, if necessary, develop harmonised rules for their surveillance.
	Improve AMR detection in the human health sector by providing EU support for networking collaboration and reference laboratory activities.
	Consider options for the harmonised monitoring of AMR in the environment, including through the network of national reference laboratories in the veterinary sector.
Benefit from the best evidence-based analysis and data	Provide evidence-based data, with the support of the ECDC, the EMA and the EFSA, on possible links between the consumption of antimicrobial agents and the occurrence of antimicrobial resistance in humans and food-producing animals.
	Define, with the support of the ECDC, the EMA and the EFSA, a limited number of key outcome indicators for AMR and antimicrobial consumption to measure the EU's and Member States' progress in the fight against AMR.
	Develop, with the support of the OECD, a model aimed at helping Member States to assess the economic burden of AMR imposes on people and to estimate the cost-effectiveness of their national policies to reduce it.
Increase awareness and understanding	Provide insights into reported public use of and knowledge about antimicrobials through Eurobarometer surveys.
	Support Member States' national awareness-raising efforts with specific communication tools targeting key audiences and contribute to the annual European Antibiotic Awareness Day (EAAD).
Improve the coordination of Member States' One Health responses to	Make available regular information on AMR in the context of the AMR One Health network, which gives an overview of the AMR epidemiological situation at Member State and EU level.
	Support the implementation of national One Health action plans against AMR through joint Commission and the ECDC visits to

Goal	Commission action
AMR	Member States upon request.
	Launch a joint action to support collaborative activities and policy development by Member States to tackle AMR and healthcare-associated infections.
	Make increased use of the EU Health Security Committee and the Commission Working Group on AMR in the veterinary and food areas to strengthen coordination and to share information.
	Seek to co-fund and collaborate with the WHO on activities to help EU Member States develop and implement national One Health action plans against AMR.
Better implementation of EU rules	Assess the effectiveness of the implementation of EU legislation on, inter alia, monitoring AMR in food-producing animal populations and food by continuing to carry out regular audits in Member States.
	Develop training programmes on AMR for Member State competent authorities under the Better Training for Safer Food (BTSF) initiative and for health professionals through the ECDC and the EU health programme.
	Advise Member States on the possibility to use the Structural Reform Support Service (SRSS) funding to Member States for designing and implementing policies against AMR.
Strengthen infection prevention and control measures	Help to address patient safety in hospital environments by supporting good practices in infection prevention and control.
	Support activities jointly funded by the EU and Member States for infection prevention and control in vulnerable groups, in particular to tackle resistant tuberculosis strains.
	Promote the uptake of vaccination in humans as a public health measure to prevent infections and subsequent use of antimicrobials.
	Continue to promote animal husbandry, including aquaculture and livestock farming systems, and feeding regimes, which support good animal health and welfare to reduce antimicrobial consumption.
Promote the prudent use of antimicrobials	Work towards EU implementing and delegated acts under the forthcoming veterinary medicinal products and medicated feed Regulations (once adopted by the European Parliament and the Council), including rules on reserving antimicrobials for human use, drawing up a list of antimicrobials that cannot be used off-label, and methods for data gathering and reporting on the sales and use of antimicrobials.
	Develop EU guidelines for the prudent use of antimicrobials in human medicine.
	Assist Member States implement EU guidelines for the prudent use of antimicrobials in veterinary medicine, including identifying and disseminating good practices.
	Encourage the EMA to review all available information on the benefits and risks of older antimicrobial agents and consider whether any changes to their approved uses in the Member States are required.
Better address the role of the environment	Adopt an EU strategic approach to pharmaceuticals in the environment.
	Maximise the use of data from existing monitoring, e.g. Watch List monitoring under the Water Framework Directive, to improve knowledge of the occurrence and spread of antimicrobials in the environment, including by using the Information Platform for Chemical Monitoring (IPCheM) to access relevant monitoring data.
	Reinforce the role of the Scientific Committee on Health and Environmental Risks (SCHER) in providing the expertise on environment-related AMR issues.
Strengthen the	Engage with and support collaboration among key stakeholders in the

Goal	Commission action
partnership against AMR and better availability of antimicrobials	human health, animal health, food, water and environmental sectors to encourage the responsible use of antimicrobials in the healthcare sector and along the food chain, as well as the appropriate handling of waste material.
	Work with stakeholders to ensure the availability of human and veterinary antimicrobials and continued access to established products; provide incentives to increase the uptake of diagnostics, antimicrobial alternatives and vaccines.
	Reduce the scope for falsified medicines by assisting Member States and stakeholders in the successful implementation of the safety features (unique identifier) that will appear by 2019 on the packaging of medicinal products for human use.
	Discuss the availability of veterinary antimicrobials to tackle AMR in the Veterinary Pharmaceutical Committee.

Source: European Commission, 2020[1]

The Action Plan also presents a series of actions associated with the goals related to the second pillar (boosting research, development, and innovation on AMR) and third pillar (shaping the global agenda). The Plan concludes by emphasizing the importance of measuring success. It proposes the development of a limited number of key outcome indicators, based on data already collected, to be developed with the support of the EU scientific agencies. They are intended to enable member states to assess, in a clear and simple way, progress made in the implementation of their national One Health action plans on AMR. The indicators are also expected to help Member States to set measurable goals to reduce infections by key antimicrobial resistant microorganisms in humans and food-producing animals, to improve the appropriateness of the use of antimicrobials in the human and veterinary sectors and to combat AMR in all sectors.

Progress will be discussed at regular intervals in the One Health network on AMR, with assessments being used to guide individual Member States and to determine if new actions are needed at EU level.

2.3. National AMR Policies in Europe

In 2018, a study by the European Public Health Alliance (EPHA) confirms the diversity in content and implementation of national action plans across 31 European nations. Only half used a One Health approach. Setting measurable targets, integrating monitoring and evaluation methods, and identifying funding sources were identified as important, according to the report, to ensure that estimated financial resources have supported national action plan implementation.[114]

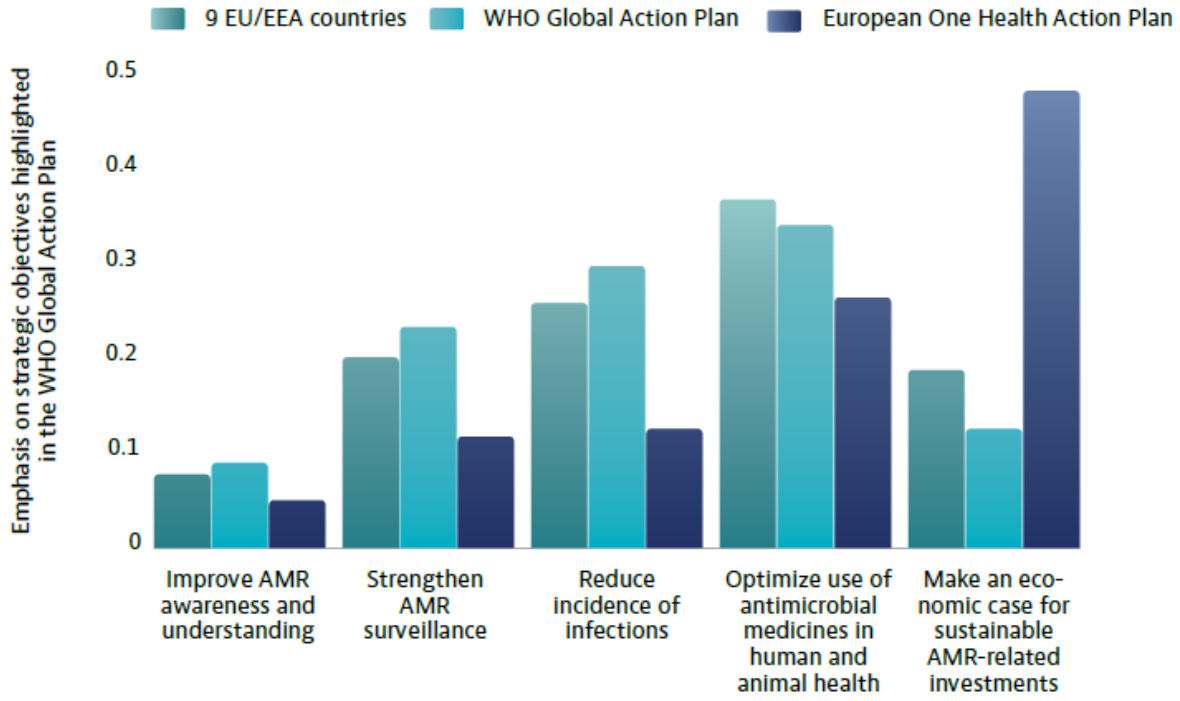
In TrACSS findings, as of May 2021, Member States report that 25 out of 29 EU/EEA countries had developed an action plan to tackle AMR. Progress on plan development and implementation are as follows:

- No national AMR Action Plan: Poland
- National AMR Action Plan is under development: Bulgaria, Estonia, Lithuania

- National AMR Action Plan developed: Belgium, Czech Republic, Slovenia, Hungary, Greece, Portugal, Romania, Cyprus
- National AMR Action Plan being implemented: Finland, Ireland, Croatia, Austria, Germany, Denmark, Netherlands, Latvia, Sweden
- National AMR action plan being implemented and actively monitored through a monitoring and evaluation framework: Slovakia, France, Italy.

An analysis of action plans from nine EU/EEA countries (based on their TrACSS 2020-2021 report) reveals that, consistent with the WHO-GAP, national action plans emphasise policies to optimise antibiotic use in human and animal health the most, followed by policies to strengthen AMR surveillance, and Infection Prevention and Control (IPC) measures.[115] These findings are displayed in **Figure 11**.

Figure 11 Comparing the content of 9 national action plans in EU/EEA countries, the European One Health Action Plan and the WHO Global Action Plan



Source: OECD Briefing Note from March 2022[115]

In May 2022, the European Commission's AMR One Health Network held a Subgroup meeting focused specifically on reviewing the content of National AMR Action Plans of the EU-27 with respect to One Health. Their review[116] reports that:

- 26 of the EU-27 countries have a One Health National AMR Action Plan.
  - 12 countries have valid and approved plans.
  - 10 countries have plans that lapse in 2022.
  - Cyprus has a plan approved prior to the adoption of WHO GAP Objectives.
  - 4 do not have valid and approved plans:
    - Hungary has a two-sectoral plan

- Estonia and Romania have a one-sector plan
- Poland does not have a National One Health AMR Plan

Even prior to the TrACCS, since 2006 and with an expanded scope after 2016, the ECDC and the European Commission's Directorate General for Health and Food Safety jointly carry out One Health' country visits. These visits are conducted only following an invitation by Member States to assist Member States in the development and implementation of their national strategy for tackling AMR based on a 'One Health' approach. The ECDC team focusses on the human health aspects of AMR, while the Commission team concerns itself with veterinary aspects and, to a limited extent, environmental aspects. Both teams include national experts from Member States. The report of the visit brings together the main observations and conclusions of the two teams and identifies areas where further developments could be beneficial. Between 2006 and 2019, AMR country visits were made to 27 EU Member States and one EEA country.[117]

The assessment instrument used in the 2020 version of the visit includes a series of indicators in the following domains: inter-sectoral coordination mechanisms, national action plans, organised multidisciplinary collaboration at local level, clinical diagnostic and reference laboratory services, monitoring of AMR, monitoring of antimicrobial consumption, antimicrobial stewardship and treatment guidelines, IPC, AMR and IPC education, public information and behavioural change interventions for AMR ("One-Health" – all sectors), and marketing issues.[118]

The resulting reports provide considerations for future actions for the country visited,[119] providing an opportunity for shared learning about strengths and weaknesses of different approaches and the ways that are most likely to succeed when implementing national action plans. Highlights from some of the most recent visits are summarized in the following paragraphs.

Ireland's commitment to the management of AMR, in all sectors, was seen, in October 2019, as a good model for other countries to follow. It had a comprehensive inter-sectoral NAP on AMR covering the years 2017-2020, with clearly defined strategic objectives and related actions, timetables, and responsibilities, albeit it lacked quantitative targets or other indicators to measure the plan's success. A 2017 Carbapenemase-producing Enterobacteriaceae (CPE) outbreak and subsequent declaration of a National Public Health Emergency on CPE raised awareness and put AMR on the agenda of all the key actors. On the other hand, the importance of maintaining control of other pathogens with AMR was emphasised, as was the prevention of HAIs in general and the long-term sustainability of the CPE control measures that had been implemented.

A March 2019 visit assessed that **Estonia** had yet to develop a One Health approach to AMR. The report noted that "the relatively limited size of the problem of AMR has led to underestimating the potential consequences that AMR could have in the future, and possibly to deprioritising the necessary measures to safeguard the healthcare system from AMR".

A visit to **Malta** in November 2018 found little progress since a previous one in 2007. Concern was voiced about low levels of public understanding of the indications for antibiotic use, associated with high levels of demand for antibiotics by patients. Concerns were also raised about the influence of the pharmaceutical industry on doctors' prescribing, associated with high levels of broad-spectrum antibiotics in particular. Other concerns arose in relation to the governance of hospitals.

A visit to **Romania** in June 2018 raised considerable concerns, including the importance of preparing a National Action Plan for AMR that would take a 'One Health' approach, a series of recommendations on aspects of diagnosis, surveillance, prevention, and control of multidrug-resistant organisms, and the need for an inter-sectoral coordination mechanism, are among the key recommendations.

A visit to **Spain** in January 2018 expressed concern that "the high levels of CPE and AMR observed were sometimes accepted, as if they were unavoidable and health professionals felt that they had done everything they could – or everything within their remit and the limit of their resources - to control the spread of CPE". Spain was one of a number of countries where responsibility for health policy is decentralized, so that plans are implemented, and in some cases developed by, regional governments. An example from Catalonia is described in Box 1.

Box 1 Regional AMR Plan – Catalonia

Within the framework of the patient safety strategy, and in accordance with the Spanish National Antibiotic Resistance Plan, the Catalan Department of Health established "PROA Cat". "PROA Cat" is a global, cross-cutting, and integrative approach that aims to reduce AMR by optimizing the prescription and use of antimicrobials, and favoring coordination between the different agents involved in the use of antibiotics in all healthcare settings in Catalonia.

PROA Cat has three main pillars: monitoring of antibiotic sensitivity, monitoring antibiotic consumption, and tailored interventions. Monitoring of antibiotic sensitivity is done locally, with the collaboration of all Catalan laboratories. Catalonia started monitoring of antibiotic sensitivity at primary care centers (adults and children) and for adult hospitalizations in 2020, and for child hospitalizations in 2021. In 2022, monitoring of antibiotic sensitivity at long-term care centers will commence. The data is returned to all professionals in the region. Tables and maps of aggregate data are provided. Tailored interventions are designed in order to adapt empirical treatments and antimicrobial therapeutic guideline recommendations to the local sensitivity values.

In addition, the consumption of antimicrobials in the adult and paediatric population is monitored. A standard surveillance system is place, which includes an AMR registry, the deployment of interventions, and monitoring of indicators in the different healthcare settings. In parallel with the tailored interventions, antimicrobials use is protocoled to

treat the most prevalent infections, promoting the use of diagnostic tools. Two educational programs are in place: one targets community pharmacies and another targets the public on the benefit of medicines and the adequate use of antibiotics.

Source: PROA Cat 2019-2025[120]

A visit to **Belgium** in November 2017 called for an increase in the sense of urgency to bring about change among prescribers and the general public, with the visitors pointing to a need for strong leadership and guidance.

The visit to **Italy** in January 2017 led to expressions of concern, as in Spain, that high levels of AMR are often accepted as unavoidable by many groups within the healthcare system. As in Belgium, the visitors urged a greater sense of urgency about the AMR situation at all levels and among all stakeholders in the country. They also emphasized the need for clear definitions of the responsibilities of those concerned, coupled with central coordination, supervision, and auditing of progress in the regions, and particularly those where the burden of AMR is greatest. Italy has developed a performance evaluation system, illustrated as a good practice in Appendix A.

2.4. Evidence regarding the effectiveness of existing policies to tackle AMR

It is challenging to ascertain the effectiveness, or cost-effectiveness, of policies to tackle AMR because (1) it is difficult to untangle the relative impact of the different types of activities that are combined with a given national action plan, (2) the impact of a specific activity depends on its implementation, and (3) the mechanisms through which a given activity leads to downstream impact are not fully clear. Despite these challenges, a 2019 Policy Brief on Averting the AMR Crisis[121] synthesizes existing evidence for the key activities related to each of the 5 strategic WHO GAP objectives. The following conclusions can be drawn from an attempt to summarize and extend the findings described in Section 1 by WHO GAP Objective and identify areas for improvement.

WHO GAP Objective 1: To improve awareness and understanding of AMR through effective communication, education and training. Although several countries experience a reduction in the number of antibiotic prescriptions following AMR awareness campaigns, the most effective public health messages and interventions are not clear. Training for professionals from health, animal, food and environmental sectors on AMR, AMS, and IPC is important. Guidance from the WHO in the form of a dedicated Competency Framework for Health Workers' Education and Training on Antimicrobial Resistance is available that outlines knowledge, skills, and attitudes for different groups.[122] Despite this, training varies in quality and coverage within and across countries.

WHO GAP Objective 2: To strengthen knowledge through surveillance and research. Surveillance data will inform the development of the national action plan and offer feedback on implementation effectiveness once established. Such systems ideally span human, animal, plant, and environmental health. National systems should link into

international ones, which require certain standards. This means ensuring adequate laboratories, equipment and technical expertise, along with regular external quality assessment. Both structures and processes must be in place for successful data collection.

WHO GAP Objective 3: To reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures. Infection Prevention and Control measures can be horizontal (applied generally across a whole institution) or vertical (address specific problems, such as a type of infection). However, it is not clear which strategy is more effective. OECD modelling suggests that improved hand hygiene would represent a particularly good investment, with an average annual implementation cost of USD PPP[2] 8500 per 100 000 persons and a net return of approximately USD PPP 140 000.[17]

WHO GAP Objective 4: To optimize the use of antimicrobial agents in human and animal health. In primary care, effective interventions to change the prescribing behaviour of clinicians use guidelines, outreach visits, clinical audit, and/or computerized reminders. Financial incentives have demonstrated effectiveness. Shared decision-making is highly effective. Rapid, affordable and easy-to-use diagnostic tools, including point-of-care tests, can be effective but are not widely available. Cost-effectiveness evidence is lacking. A Cochrane review of hospital AMS programs has shown that those involving enablement (e.g., the use of audit and feedback) and/or restrictive techniques (e.g., the use of rules and guidelines) are most effective.[51] However, better quality cost-effectiveness evidence is needed.

WHO GAP Objective 5: To 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. OECD modelling suggests that effective implementation of AMS programmes could result in a 51% reduction of deaths from AMR and EUR 2.3 billion saved.[123] The OECD Strategic Public Health Planning for AMR (SPHeP-AMR) model will compare health and economic impact of a number of AMR control policies relative to a business-as-usual scenario without interventions.

2.5. Effective implementation of national action plans

To assist nations in developing new and improving existing national action plans, the WHO created a guidebook to assist nations in developing new and improving existing national action plans. Other resources for nations include sample terms of reference for

[2] United States Dollar (USD) purchasing power parity (PPP) is used to equate currencies between countries, based on the currency's purchasing power for a select basket of goods in each respective country.

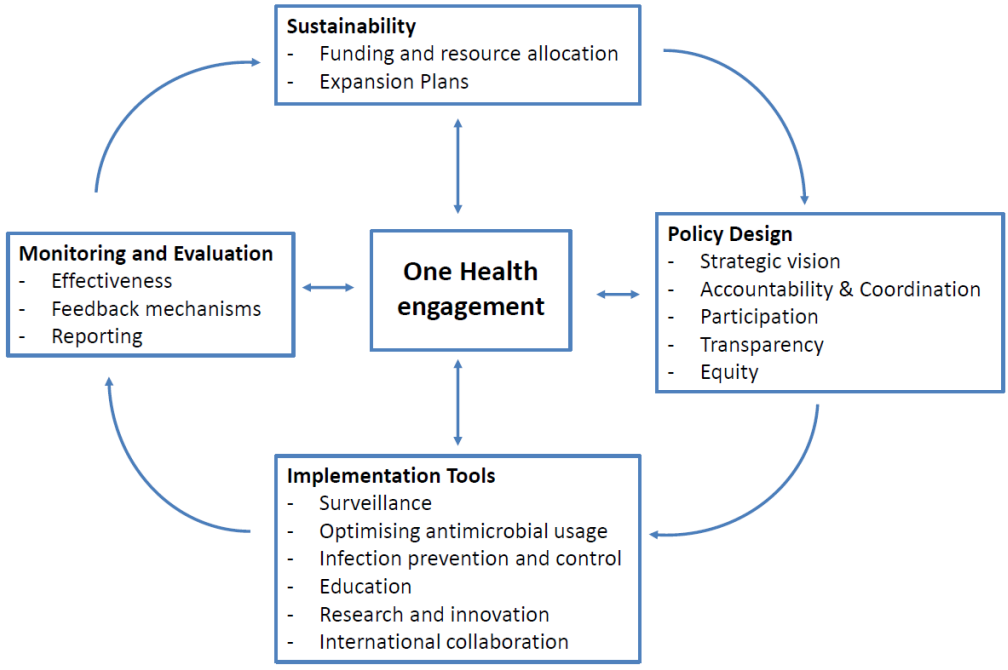
suggested coordination mechanisms, a generic template for a national action plan, a sample monitoring and evaluation plan, and a checklist produced by WHO in partnership with FAO and WOAH (OIE) to accompany this manual.[124]

Yet, according to the Interagency Coordination Group (JACG) on Antimicrobial Resistance's 2018 report, the greatest challenge in most countries is not writing or developing the national action plan, but implementing it in a sustainable manner. Barriers include lack of awareness and political will, finance, coordination, monitoring and data, and technical capacity. It was established that good AMR policy governance is a significant determinant of success.[125]

In 2019, the European Observatory on health systems and policies echoed this finding. Besides emphasizing the importance of comprehensiveness in national action plans, they indicated that implementation is the most difficult aspect of combatting AMR. Specific conditions must be in place and strong governance is a critical factor in achieving success.[121]

A governance framework with 18 domains and 52 indicators has been found to be useful to address the dynamic nature of AMR. The framework is divided into three governance areas: "policy formulation," "implementation tools," and "monitoring and evaluation." The framework is designed as a cyclical process that is responsive to the context and enables for continual refinement and adaptation of AMR national action plans (**Figure 12**). [80] This approach has been used to analyse national action plans in Southeast Asia as a proof of concept.[126]

Figure 12 Framework for continuous improvement and adaptation of national action plans for AMR



Source: Anderson et al. 2019[121]

Part of Monitoring and Evaluation involves the selection of appropriate indicators. Developing indicators and targets for AMR action plans in the EU was one of the key recommendations ("calls to action") resulting from the Joint Action EU-JAMRAI. Between 2017 and 2021, the EU-JAMRAI Project mapped and assessed participating countries, adopted a WHO tool for the EU, implemented infection prevention and control frameworks in five countries, and published a set of AMR guidelines for European countries.[127] The AMR Policy Analysis Coding Tool is a potential solution. It is a quantitative technique for national action plan policy analysis.[128] The tool provides empirical results that may be used as indicators of a country's priorities and AMR policy gaps. It may also help to create an AMR policy database and stimulate innovative policymaking in this way.

In February 2022, the WHO published a comprehensive implementation handbook for national action plans specific to the human health sector.[129] The handbook focuses on implementation and monitoring and evaluation and emphasizes multisectoral governance. It offers 6 steps for sustainable implementation of national action plans:

1. Strengthen governance
2. Prioritize activities
3. Cost the operational plan
4. Mobilize resources
5. Implement prioritized activities
6. Monitor and evaluate

The chapters provide insight into the structures to be put into place and the processes or capacity building required. The handbook also provides links to existing tools to use to effectively carry out the recommended steps.

Concrete implementation strategies for Member States to effectively carry out existing and planned policies to tackle AMR

Part of implementation of a national action plan requires consideration of the conditions for successful deployment of a given single intervention or group of multiple interventions (also termed a packaged programme). Strategies that influence the effectiveness of specific AMR intervention have been examined, for instance, specifically with respect to POCT. For instance, type of instrument, the number of times performing external quality assurance (EQA) exercises, performing internal quality control (QC) weekly, performing 10 or more tests weekly, and having laboratory-qualified personnel perform the tests were associated with good point-of-care test performance.[130] Similar factors should be examined and systematically evaluated for each component of the national action plan implemented.

Good practice recommendations with respect to POCT implementation include use multi-dimensional checklist and multidisciplinary teamwork.[131] Several areas need to be covered such as technical description of the test, clinical pathway, patient stakeholders, economic evidence, test performance, usability and training. Another good practice with respect to POCT is Belgium's POCT framework, which is based on 4 priorities: (1) Extend the Belgian decree on certification of clinical laboratories to decentralised tests in primary care; (2) Introduce a separate reimbursement category for POCT; (3) Introduce reimbursement for a limited number of specified point-of-care tests; and (4) Set-up a Multidisciplinary POCT Advisory Council, the purpose of which is to draw up a model for reimbursement of POCT, to select tests eligible for reimbursement and to make proposals to the National Institute for Health and Disability Insurance (RIZIV/INAMI).

General implementation strategies

The field of implementation science has dedicated research efforts on understanding implementation strategies. These strategies are separate from an intervention, programme, or practice and can be defined as the "methods or techniques used to enhance the adoption, implementation, and sustainability of a clinical program or practice".[132] They are proposed as a way to bridge the research-to-practice gap. A number of taxonomies of implementation strategies exist. The Expert Recommendations for Implementing Change (ERIC) study generated expert consensus on implementation strategies via a three-round modified Delphi process that refined prior work.[133] The result was a final compilation of 73 discrete ERIC strategies with definitions that represent a range of possible strategies that can be used to implement new programmes and practices. Specific strategies may be selected based on a particular conceptual framework underlying implementation (e.g., the Consolidated Framework for Implementation Research (CFIR)[134] or Promoting Action on Research Implementation in Health Services (PARIHS) framework.[135] Box 2 identifies some key ERIC strategies deemed by the EXPH drafting group to be relevant to implementation of national action plans to tackle AMR.

Box 2 Common useful implementation strategies for systemic deployment to tackle AMR

1. Build health information technology to support data-informed quality improvement
- Adapt and tailor to context (e.g., via stakeholder input)
- Use evaluative iterative strategies (e.g., audit and feedback, Plan-Do-Check-Act cycles)
- Utilize financial strategies (e.g., funding and contracting)
- Change infrastructure (e.g., records systems)
- Provide interactive assistance (e.g., from local, trusted sources)

2. Build quality improvement (QI) capacity and improve outcomes
- Provide interactive assistance (e.g., context-specific implementation facilitation)
- Use evaluative iterative strategies (e.g., identify barriers and enablers, develop a local implementation blueprint or plan)
- Support clinicians (e.g., reminders and regular contact)

- Develop stakeholder inter-relationship (e.g., identify clinician champions of the program)
- Engage consumers / patients (e.g., develop patient educational materials)

3. Enhance clinician and practice member knowledge
- Train and educate stakeholders (e.g., develop and distribute educational materials, conduct outreach visits, provide on-going consultation and training)
- Develop stakeholder inter-relations (e.g., visit other sites to share best practices)

4. Build connections across the health system (*adapted for AMS*)
- Support clinicians (e.g., develop resources sharing agreements across facilities in the health system)
- Engage consumers / patients (e.g., include diverse stakeholders – hospital, primary care centres and long-term care facilities - and patients on QI teams)
- Use evaluative and iterative strategies (e.g., obtain and use feedback from stakeholders)

Source: Author's compilation based on ERIC implementation strategies [133] clustered by functional group [136]

Each region or country will likely need different implementation strategies that are adapted or tailored to their needs. Therefore, it may also be useful for countries to develop a logic model, which is a type of programme theory evaluation hypothesizing the proposed casual mechanisms through which a strategy is purported to induce change in the health system.[137] The systematic approach to selecting implementation strategies emphasizes the context-dependent nature of effective systemic deployment of national plans and an area of future development.

3. Recommendations

In developing our recommendations, we recognise the considerable work that has already taken place, and in particular, the commitments set out in the 2017 European One Health Action Plan on AMR,[1] which we fully endorse. Consequently, we do not seek to repeat what is in that plan, but rather to go beyond it.

Recommendation 1: All member states should ensure that they have comprehensive, up-to-date National Action Plans to tackle AMR and robust governance arrangements in place to implement them.

This Opinion has described how AMR arises because of failures in many sectors, individually, and collectively. Tackling these failures poses many challenges, given the multitude of actors involved. Following the 2015 WHO Global Action Plan Member on AMR[110] and the 2016 Council Conclusions on a One Health approach to AMR,[113] most Member States have published National Action Plans. However, these vary in their content and form, with not all adhering to the recommendations developed by WHO.[124]

While a pre-requisite for success is the existence of a comprehensive and up-to-date National Action Plan, it is also necessary to have robust governance systems within member states, encompassing healthcare, science and technology, and agriculture and food, covering the public and private sector and all tiers of government, and with strong international links. The precise arrangements needed are, of course, a matter for each member state, reflecting the different ways that they organise these sectors and, especially for the smaller member states, their domestic capacity. What is important, however, is that these arrangements are clearly understood by all concerned.

There are certain key elements to any system of governance.[138] First, there must be *transparency*, with near real-time reporting of data on AMR (see recommendation 3) and on the conditions that give rise to it. Clear lines of *accountability*, whereby one individual or organisation has the duty to account for progress to the domestic executive and legislature and to European and international institutions. The system must be *participatory,* ensuring that all relevant stakeholders and factors are included. The system must have *integrity*, underpinned by an appropriate legal framework and measures to enforce compliance where required. There must be *capacity,* to monitor the situation, identify problems, and act on them, which in many cases will require sustained investment in laboratories, surveillance, and clinical governance.

Recommendation 2: While recognising the different competencies given to the European Union by the Treaties in the areas of human and animal health, we recommend that the European Commission be more ambitious in taking advantage of the opportunities that exist within the full range of EU legal instruments to bring the two together, consistent with the concept of One Health.

The Expert Panel understands the historical and political reasons why animal and human health have been treated differently in the Treaties, reflecting the differing implications for the single market and the application of the principle of subsidiarity. However, these differences are of no concern to the microorganisms that move between humans and animals. The Expert Panel notes, with approval, measures that have been adopted to restrict the use of some antibiotics to humans, enacted under food safety provisions.[139] The requirement that *"A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities"*, set out in Art. 168 TFEU, coupled with the 2016 Council Conclusions on a One Health approach offers the potential to do more to develop a One Health approach to AMR, through legislation where this is possible but, where it is not, through other measures, including research and the exchange of knowledge.

Recommendation 3: The European Commission should prioritise the development of a comprehensive set of indicators and structured data to measure progress on tackling AMR, ensuring that they are integrated in data collection requirements embedded in relevant regulatory frameworks.

The European Commission, in its Action Plan on a one health approach to AMR, committed to "*define, with the support of the ECDC, the EMA and the EFSA, a limited number of key outcome indicators for AMR and antimicrobial consumption to measure the EU's and Member States' progress in the fight against AMR"*. However, as noted in a 2019 report by the Court of Auditors,[140] *"Outcome indicators were not consistently used by the Member States we visited, or by the Commission, to monitor progress; data on health care associated infections, which are the primary source of AMR infections, was incomplete; and, at the time of our audit, there was insufficient knowledge about AMR in the environment".*

It is essential that this is prioritised but beyond the commitment in the Action Plan. The Expert Panel recommends that these are integrated in relevant regulatory frameworks. [141] [142] [140]

Recommendation 4: Member States should focus research on understanding why policies and practices on their territories continue to create risks of AMR and the European Commission should support exchange of the knowledge thus generated.

The biological mechanisms that allow the emergence and spread of AMR are well understood so the continuing threat that AMR poses is a failure of policies and practices. However, the incentives that underlie these failures and the barriers to overcome them will vary across the many settings in which antimicrobials are used. These include pressures on food producers to cut costs of production, leading to poor hygiene practices, inadequate infection control in health settings, and inappropriate prescribing. Moreover,

there is a need to explore innovative solutions e.g. in the field of R&D for development of new antibiotics, testing, and medical technologies.

The Expert Panel recommends that member states establish programmes of research that seek to understand the structural factors that underlie inappropriate practices (e.g., in prescribing and infection prevention and control), and how they can be overcome. Such research programmes include clinical decision-making in conditions of uncertainty and the effective integration of innovations in testing and medical technologies into clinical practice. Other topics are related to the expansion of roles of pharmacists and others. It is considered valuable to use of insights from behavioural sciences and policy analysis to change behaviour of those using antimicrobials and those creating the conditions in which they are used. Furthermore, insights from psychology and marketing research can inform the development of messaging to practitioners (including academic detailing), health policy makers, and the public to ensure the appropriate use of antimicrobials.

Recommendation 5: The European Commission should conduct a foresight exercise to inform future policy on AMR.

Foresight exercises offer a means to convene expert knowledge to develop potential future scenarios and to develop responses to them. The Expert Panel calls on the European Commission (in an initiative that brings together relevant Directorate Generals) to identify conditions now and in the future (for example arising from climate change or loss of biodiversity) that increase the risk of AMR, as well as gaps in the existing portfolio of products that can support rapid differential diagnosis of infections and can prevent and treat them.

LIST OF ABBREVIATIONS

ACR	Acrosin
AMR	Antimicrobial resistance
AMS	Antimicrobial Stewardship
ATC	Anatomic Therapeutic Chemical (classification code)
BTSF	Better Training for Safer Food
CFIR	Consolidated Framework for Implementation Research
CMg	Clinical Metagenomics
CPE	Carbapenemase-producing Enterobacteriaceae
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRP	C-Reactive Protein
DALY	Disability Adjusted Life Year
DDD	Defined Daily Doses
DNA	DeoxyriboNucleic Acid
EAAD	European Antibiotic Awareness Day
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
eCDDS	Electronic clinical decision support systems
EFSA	European Food Safety Authority
EJP	Joint Programme
EMA	European Medicine Agency
EPHA	European Public Health Alliance
EQA	External Quality Assurance
ERIC	Expert Recommendations for Implementing Change
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
EU/EEA	European Union / European Economic Area
FAO	Food and Agriculture Organisation
GAP	Global Action Plan
GP	General Practitioner
HERA	European Health Emergency Preparedness and Response Authority
ICU	Intensive Care Unit
IDS	Infectious Diseases Specialist
IL-6	Interleukin-6
IPC	Infection Prevention and Control
JACG	Interagency Coordination Group
JPIAMR	Joint Programming Initiative on AMR
MDRO	MultiDrug-Resistant Organism
mNGS	Metagenomic next-generation sequencing
MRSA	Methicillin-Resistant *Staphylococcus aureus*
NA	Not available
NIHDI	Belgian National Institute for Health and Disability Insurance
NNT	Number Needed To
OECD	Organization for Economic Cooperation and Development
PARIHS	Promoting Action on Research Implementation in Health Services
PCT	Procalcitonin
POCT	Point-Of-Care Testing
Pro-AG	Pro-Active Genetic system
QC	Quality Control
QI	Quality Improvement
RCT	Randomised Controlled Trial
RNA	RiboNucleic Acid
RTI	Respiratory Tract Infection
SDG	Sustainable Development Goal
SPHeP	Strategic Public Health Planning
TrACSS	Tripartite Annual Country Self-Assessment Survey
UI	Uncertainty Interval
UltraPro	Ultrasonography point-of-care tests

UNEP	United Nations Environmental Programme
UTI	Urinary Tract Infection
WGS-AST	Whole-Genome Sequencing for Antibiotic Susceptibility Testing
WHO	World Health Organization
WOAH	(founded as OIE) World Organisation for Animal Health

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ANNEX

Performance Evaluation System in Italy

In Italy, MeS Lab monitors antibiotics' consumption: 1) at the inter-regional level; 2) at regional level; and 3) through ad hoc analysis. The Inter-Regional Performance Evaluation System[142] currently encompasses the following indicators:

- Antibiotic consumption (community)
- Antibiotic consumption - under 14 years of age (community)
- Cephalosporin consumption - under 14 years of age (community)
- Quinolone antibiotic consumption (community)
- Injectable antibiotics proportion (community)
- Antibiotic consumption (hospital)
- Quinolone antibiotic consumption (hospital)
- Carbapenem consumption (hospital)
- Injectable antibiotics proportion (hospital)

Five of the previous indicators are not only monitored, but rather benchmarked against standards that have been agreed by the Inter-Regional Performance Evaluation System. Standards are set according to the Italian Local Health Authorities' performance, and by comparing it with international performance. Table 7 reports the standards agreed in 2021.

Table 7 Benchmarking Standards for Antibiotic Consumption per Italian Local Health Authorities

Indicator	**Metric**	**Red band (bad performance)**	**Orange band**	**Yellow band**	**Light green band**	**Green band (great performance)**
Antibiotic consumption (community)	DID	>25.50	22.50-19.50	19.50-16.50	16.50-13.50	<11.50
Antibiotic consumption - under 14 years of age (community)	DID	>28.00	28.00-23.60	23.60-19.20	19.20-14.80	<14.80
Cephalosporin consumption - under 14 years of age (community)	DID	>4.20	4.20-3.10	3.10-2.00	2.00-0.90	<0.90
Quinolone antibiotic consumption (community)	DID	>2.40	2.40-1.90	1.90-1.50	1.50-1.00	<1.00
Injectable antibiotics	%	>2,30	2,30-	1,80-	1,20-	<0,70

proportion (community)			1,80	1,20	0,70	

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Ad hoc analyses are performed by MeS Lab. Figure 20 shows example data available. Current indicators include:

- Proportion of Access antibiotics out of total antibiotic consumption
- Proportion of Reserve antibiotics out of total antibiotic consumption
- Local expenditure on antibiotics (per capita consumption and average cost per DDD)

Some of the previous indicators have been monitored and included in the Tuscan pay for performance scheme for Health Authorities' CEOs, as detailed in Table 8.

Table 8 Indicators used for monitoring and pay for performance scheme in Tuscany, Italy

Indicator	**Level**	**Year**	**Goal**
Antibiotic consumption	Community	2016	Less than or equal to 18 DDD per 1000 inhabitants per day
Antibiotic consumption	Community	2017	Less than or equal to 18 DDD per 1000 inhabitants per day
Antibiotic consumption	Community	2018	Less than or equal to 18 DDD per 1000 inhabitants per day
Antibiotic consumption	Community	2019	Less than or equal to 16.5 DDD per 1000 inhabitants per day
Antibiotic consumption	Community	2020	Less than or equal to 16,5 DDD per 1000 inhabitants per day
Antibiotic consumption	Community	2021	Less than or equal to 16.5 DDD per 1000 inhabitants per day
Quinolone antibiotic consumption	Community - Hospital	2021	Reduction compared to 2019
Carbapenem consumption	Hospital	2021	Reduction compared to 2019
Incidence of amoxicillin	Community	2021	Reduction compared to 2019
Injectable antibiotics proportion	Community	2021	Increase of 50 percent compared to 2019
Consumption of carbapenems	Community and Hospital	2022	Reduction compared to 2019
Consumption of amoxicillin	Community and Hospital	2022	Reduction compared to 2019

Consumption of quinolones	Community and Hospital	2022	Reduction compared to 2019
Antibiotic consumption	Community	2022	Less than or equal to 16.5 DDD per 1000 inhabitants per day

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