ANTIMICROBIAL RESISTANCE IN THE EU

A Comparative Analysis of National Action Plans in Italy, the Netherlands and Spain

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CONTENTS

1. INTRODUCTION

Antimicrobial Resistance: A Public Health Problem

Antimicrobial resistance (AMR) occurs when microorganisms, including bacteria, viruses, fungi and parasites, become able to adapt and grow in the presence of medications that once impacted them.[1] The European Centre for Disease Prevention and Control (ECDC) reported that resistant bacteria infect almost two million people in the European Union (EU) yearly, leading to 30,000 deaths annually.[2] AMR costs the EU about €1.5 billion per year in healthcare costs and productivity losses.[3]

Building Policies

In 2015, the World Health Assembly adopted a Global Action Plan (GAP) on AMR. This action plan underscores the need for an effective One Health approach involving coordination among the international sectors and actors, including human and veterinary medicine, agriculture, finance, environment, and well-informed consumers.[4]

Within the EU, 25 of the 30 EU/European Economic Area (EEA) countries have a national action plan (NAP) on AMR. However, in 2021 only eight countries were implementing these plans and tracking performance using monitoring and evaluation (M&E) frameworks.[5] Differences in countries' NAPs exist with regards to their One Health approach, content, and level of detail, especially with regards to resources, operationality, monitoring and evaluation.[6]

In 2017, the World Health Organization (WHO) listed 12 families of bacteria that pose the greatest threat to human health. The WHO identifies three categories according to the need to develop new antibiotics to combat these pathogens: critical, high and medium priority. The critical priority group includes multidrug resistant bacteria that pose threats to patients in hospitals and nursing homes, as well as to patients whose conditions require medical devices such as ventilators and blood catheters.[7] High priority category includes bacteria that are resistant to various antibiotics, such as vancomycin and fluoroquinolones. In the medium priority are bacteria that although may have some resistance, effective antibiotics are still available that can kill them.[8] The only pathogen that does not appear on the WHO list that the ECDC monitors is *Enterococcus faecalis*. The rest, that ECDC monitors based on the WHO categorisation, are shown in Table 1.[9]

Table 1. Pathogens monitored by the ECDC

Priority category	Pathogens	Antibiotic resistance	Gram stains
Critical	*Acinetobacter ssp*	Carbapenem	Negative
	Pseudomonas aeruginosa	Carbapenem	Negative
	Klebsiella pneumoniae	3rd gen cephalosporin	Negative
	Escherichia coli	3rd gen cephalosporin	Negative
High	*Enterococcus faecium*	Vancomycin-resistant	Positive
	Staphylococcus aureus	Methicillin + vancomycin intermediate and resistant	Positive
Medium	*Streptococcus pneumoniae*	Penicillin-non-susceptible	Positive

The WHO recognised AMR as one of the top threats to global health in 2019.[7] However, AMR rates continue to increase, progress on infection prevention and control (IPC) programmes remains limited, and there has been little or no reduction in antibiotic consumption outside of a few high-income countries (HICs). Moreover, recent reviews highlight that the majority of the resulting national AMR strategies are underfinanced and prioritise short-term reactive and surveillance/monitoring approaches rather than the longer-term preventive measures also recommended by the GAP.[10, 11]

2. OBJECTIVES

This paper details a case study of a review of the NAPs in **Italy**, **the Netherlands** and **Spain**. Its goal is to better understand the epidemiology related to AMR in the three countries. Then their NAPs are evaluated and compared. Finally, this paper formulates recommendations to improve the NAPs and their implementation. More effective NAPs will help tackle AMR.

3. THEORETICAL FRAMEWORK

It is expected that AMR rates are increasing in the three countries studied, since rates are rising across Europe as a whole.[12] In addition, Southern Europe is strongly impacted by this.[13] It is also expected that all the NAPs are written under a One Health perspective.[6] As new NAPs have been released in Spain and Italy after the EU assessment tool was first applied in 2021, both Spain and Italy will likely perform better than the Netherlands.[6] However, it is also expected for the Netherlands to perform generally well as previous analyses suggest.[14]

4. METHODOLOGY

4.1. Understanding the Epidemiology Related to Antimicrobial Resistance

To see the at what level the countries are in relation to resistance from an epidemiological point of view, multiple indicators were considered. These are: consumption of antibiotics both in hospitals and in the community, the sales and use of veterinary agents, and the prevalence of healthcare-acquired infections. The three indicators' use ECDC data. This was followed by a descriptive and comparative analysis of the data.

4.2. Comparing National Action Plans to Fight Antimicrobial Resistance

To assess the NAPs, a modified assessment tool developed by the European Commission in the Overview report of the *Member States' One Health National Action Plans against Antimicrobial Resistance* was used.[6] This tool takes into account the WHO/Food and Agriculture Organization/World Organization for Animal Health manual for developing NAPs, Tripartite survey and ECDC assessment tool.[6] With this tool, a qualitative comparative analysis was carried out in which the presence or absence of the indicator under study was taken into account. In the presence of the indicator, it was then considered if it was up to date and whether its relative quality was assessed in the NAP. Quality of an indicator usually takes the form of a clear action plan that sets specific, measurable, achievable, relevant and time-bound (or SMART) goals.[15] Taking all these factors into account, a colour scale was developed to better understand NAPs' compliance with the assessment tool: red when the item was absent in the NAP, orange when it was mentioned but of clearly inferior quality, and green when the item was in place in the NAP and of considerable quality. To calculate compliance and compare countries with each other, a subsequent quantitative comparative analysis was performed in the form of percentage of compliance using a point system: 1 for green, 0.5 for orange and 0 for red.

5. RESULTS

5.1. Understanding the Epidemiology Related to AMR

5.1.1. The epidemiology of resistance, total

Figure 1. Antibiotic resistance (%) from 2005 to 2021 in Italy, Spain and the Netherlands

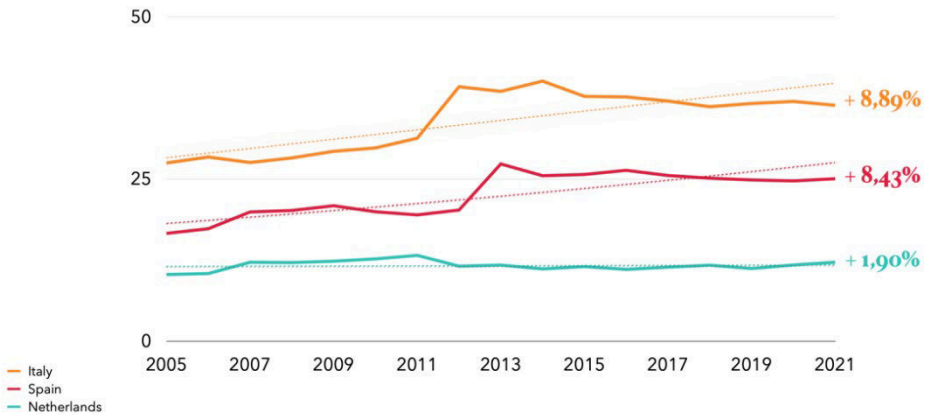
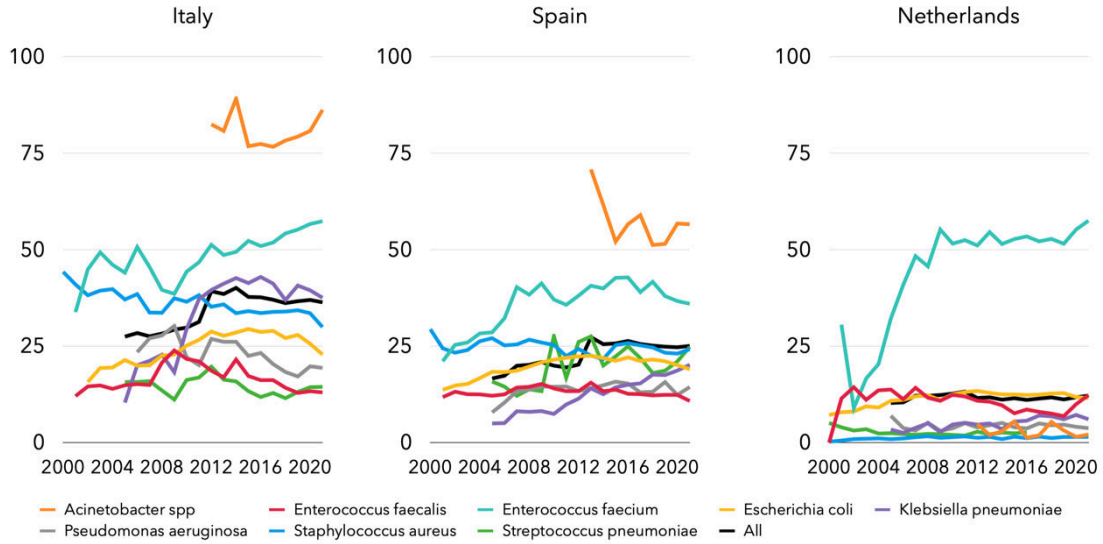


Figure 1 shows the data on the evolution of antimicrobial resistance from 2005 to 2021. Data prior to 2005 were not taken into account since the number of microorganisms on which data was collected were few and distorted the general evolution trend.

Compared to 2005, there has been a general increase in AMR. However, this increase is much higher in Italy and Spain than it was in the Netherlands. Overall AMR average is highest in Italy (34%), followed by Spain (22.7%) and the Netherlands (11.7%). However, the increase in Italy and Spain is directly related to the introduction of *Acinetobacter spp.* surveillance in 2012 (Figure 2), where a clear increase in the average resistance can be seen. This is not the case in the Netherlands, where the largest increase in the average is due to *Enterococcus faecium* (Figure 2).

5.1.2. The epidemiology of resistance

Figure 2. Antibiotic resistance (%) from 2000 to 2021 by microorganism in Italy, Spain and the Netherlands



Overall, Italy had an increase in resistance to antibiotics over the years (see Figure 1). From 2005 to 2020, the year in which a greater number of microorganisms began to be monitored in Italy, resistance has increased by 8.9%. In 2021, 86.2% of *Acinetobacter spp*, a WHO critical priority category bacterium, were resistant strains. Another microorganism that has a high level of AMR *is Enterococcus faecium*, whose resistance was 57.4% in 2021.

As is the case in Italy, resistance against antibiotics also increased in Spain—by 8.5% since 2005 (see Figure 1). As in Italy, resistance for *Acinetobacter spp* is high at 56.6%, but has decreased since the monitoring began. *Enterococcus faecium* also had a high level of AMR (36.0%). However, when looking at the trend of AMR in these two strains more recently, it seems that in recent years a decline in AMR can be observed.

Unlike in Italy and Spain, in the Netherlands *Acinetobacter ssp* has a much lower resistance rate (see Figure 1). In the Netherlands, 2.1% of *Acinetobacter spp* was resistant to antibiotics, compared to 56.6% in Spain and 86.2% in Italy. Furthermore, most pathogens in the Netherlands have an AMR rate below 12.5%. The only microorganism that has a high AMR

rate in comparison is the *Enterococcus faecium*, with 57.5% of strains resistant to some type of antibiotic. Interestingly, this is higher than the rates found in Italy and Spain.

5.1.3. The epidemiology of antibiotic consumption

Figure 3. Antibiotic consumption in Italy, Spain and the Netherlands

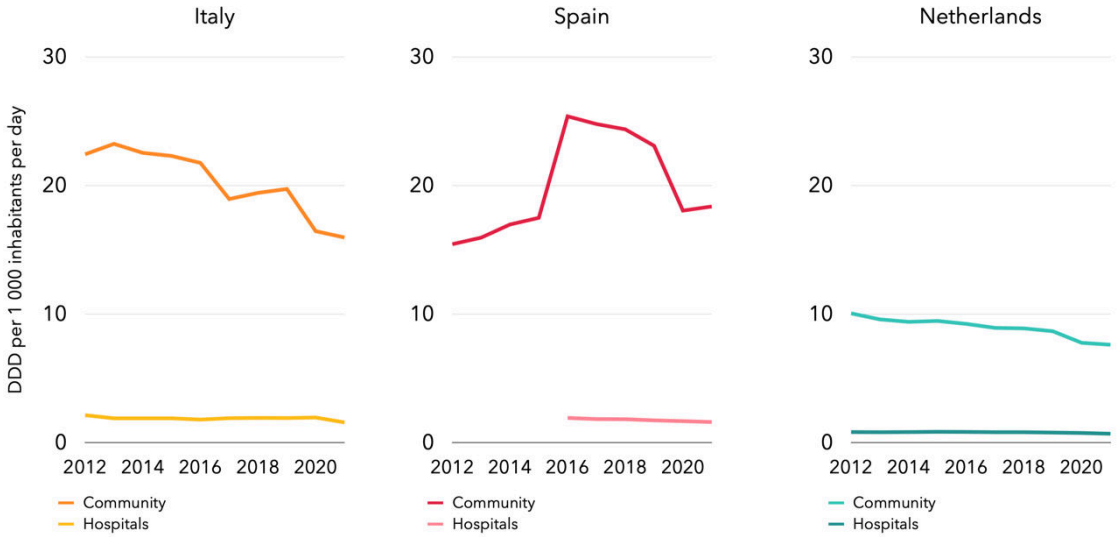
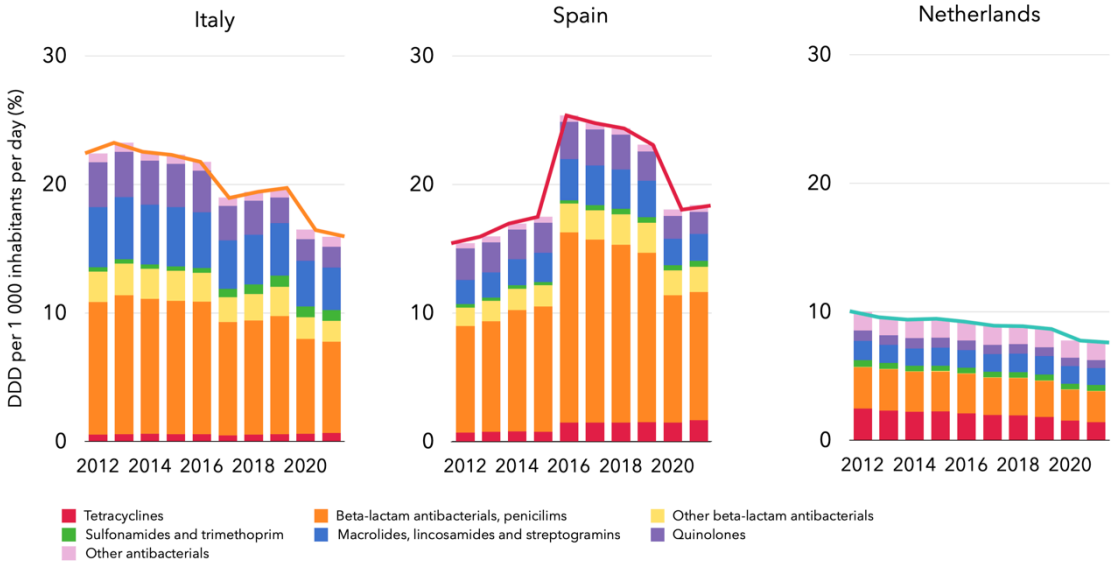


Figure 3 shows antibiotic resistance in Italy, Spain and the Netherlands in defined daily dose (DDD) per 1,000 inhabitants per day. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO). It is a unit of measurement that was created to facilitate comparison between countries.
The consumption of antibiotics is much higher in the community than in hospitals since the population is much smaller in hospitals than in the community. The use of antibiotics is similar between Italy and Spain when compared to the Netherlands, which has a clear downward trend and a much lower use of antibiotics in both community and hospitals. (Figure 3). This is extremely important because the use of antibiotics is related to the prevalence of antimicrobial resistance. Therefore, the data available in Figure 3 is closely related to the resistance data of Figure 2. In fact, one of the most important elements of NAPs strategies focus precisely on this point.

Figure 4. Antibiotic consumption in Italy, Spain and the Netherlands from 2012–2021 by antibiotics in the community

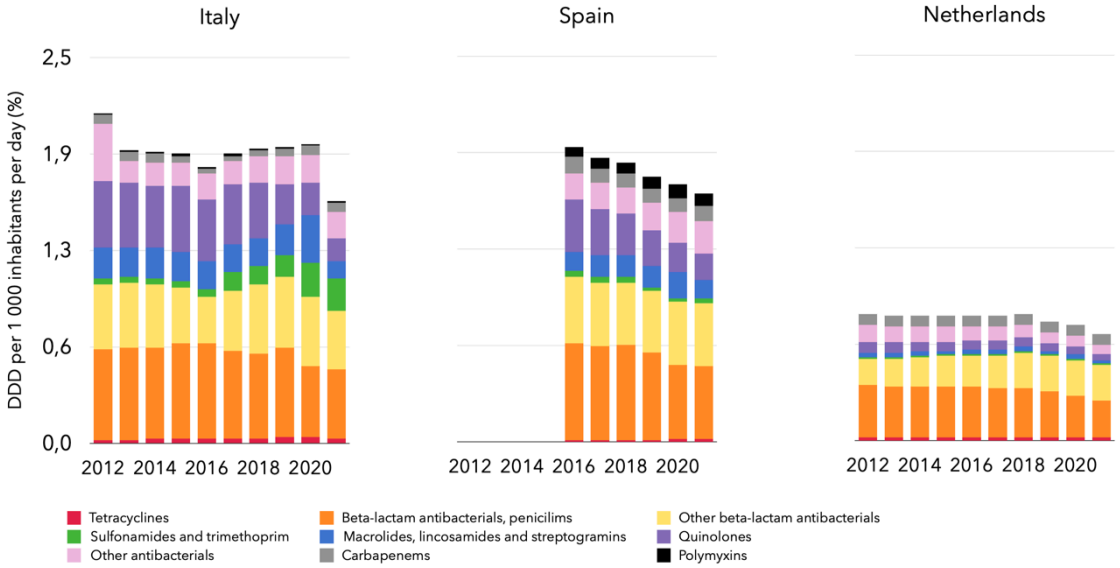


In Italy, the use of antibiotics in the community has been decreasing over the years (see Figure 4). In 2021, the DDD per 1,000 inhabitants was 15.93, which is a reduction of 28.9% compared to 2012. The reduction in the use of penicillin stands out, which decreased 31.1% compared to 2012.

In Spain, the use of antibiotics has increased over the years by 2.93 DDD per 1,000 inhabitants per day, reaching 18.37 DDD per 1,000 inhabitants per day in 2021 (see Figure 5). The consumption of antibiotics in the community is higher in Spain than in Italy. The use of antibiotics in 2016 is noteworthy as it increased 45.1% compared to the previous year. However, Spain has been doing better in recent years, with a decline in antibiotic use seen in the years following the COVID-19 pandemic.

As was the case with antibiotic resistance, the consumption of antibiotics in the Netherlands is below that of the other two countries (see Figure 6). What is more, its use has been declining over the years. This decrease is mainly due to the decreasing use of penicillin and tetracyclines. Compared to 2012, in 2021 the use of antibiotics fell by 2.44 DDD per 1,000 inhabitants per day, reaching a total of 7.59 DDD per 1,000 inhabitants per day. In the same year, the DDD per 1,000 inhabitants was 14.43 in Italy, and 18.37 in Spain.

Figure 5. Antibiotic consumption in Italy, Spain and the Netherlands from 2012–2021 by antibiotics in hospitals



In hospitals in Italy, the decrease compared to 2012 has not been as significant as it has been in the community. Furthermore, the consumption of antibiotics over the years has remained fairly stable. The consumption of antibiotics in hospitals in Spain has a clear downward trend. Note the absence of data in Spain from 2012 to 2016, during which Spain did not report data to the ECDC.

The use in the hospital setting in the Netherlands is also much lower than in Italy and Spain; the consumption of DDD antibiotics per 1,000 inhabitants per day is 1.57 in Spain, 1.60 in Italy, and 0.69 in the Netherlands. Again, the low use of tetracyclines is observable in the Netherlands, especially compared to the other two countries.

5.1.4. The epidemiology of antibiotic sales for food producing animals

Figure 6. Antibiotic sales for animal use in Italy, Spain and the Netherlands from 2010–2021

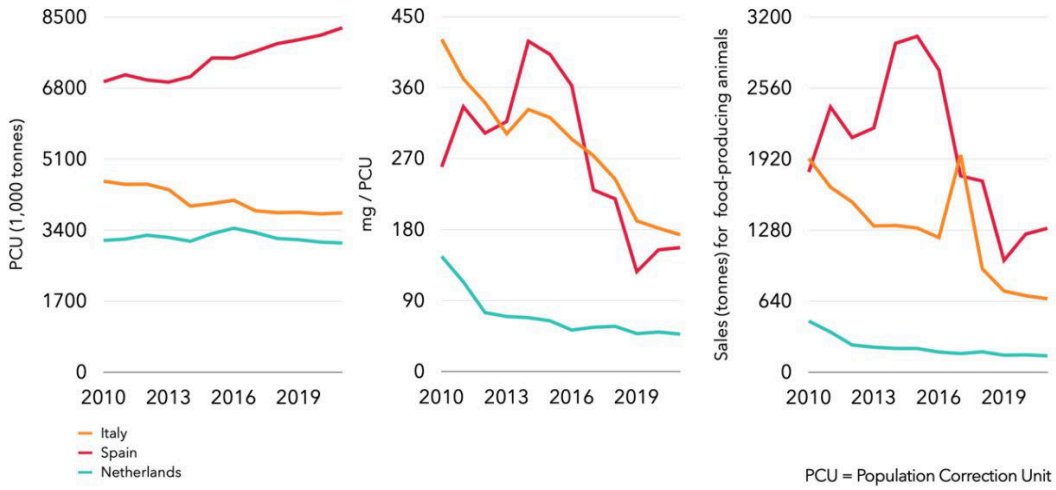


Figure 6 shows the sale of antibiotics for food producing animals and its relation to the population correction unit (PCU) use in Italy, Spain and the Netherlands: PCU per 1,000 tonnes, sales in milligram of active substance sold by PCU (mg / PCU) and sales of all antibiotic active substances (tonnes) for food-producing animals.

Between 2010 and 2021, sales in mg/PCU of active ingredients of veterinary antimicrobial agents marketed mainly for food-producing animals (including horses) decreased by 58.8% in Italy, by 39.4% in Spain, and by 67.4% in The Netherlands (see Figure 7). Sales in PCU decreased by 16.6% and 2.0% in the same period in Italy and the Netherlands, respectively, while it increased by 18.6% in Spain. Finally, sales in tonnes also decreased by 65.6% over those years in Italy, by 28.2% in Spain, and by 68.1% in The Netherlands.

5.1.5. The epidemiology of healthcare-acquired infections

In Italy, the prevalence of healthcare-acquired infections (HAIs) stands at 8.0 (6.8-9.5), with the most common types being pneumonia (23%), urinary tract infections (18%), and surgical site infections (18%). In the Netherlands, the prevalence of healthcare-acquired infections is 3.8 (3.4-4.3), with surgical site infections being the most frequent at 35%, followed by urinary tract infections (24%), and pneumonia/Lower Respiratory Tract (LRT) infections at 17%. Meanwhile, in Spain, the prevalence of healthcare-acquired infections is 7.8 (7.0-8.5), with surgical site infections accounting for 26% of cases, followed by urinary tract infections and pneumonia/LRT infections, both at 20%.[16]

5.2. Comparing National Action Plans to Fight AMR

The various NAPs were evaluated using the EU tool.[6] In the following section, the strengths, weaknesses, and points for improvement of each of the NAPs will be reviewed and compared to each other. Overall, Italy meets 72% of the requirements of the NAP evaluation tool, the Spain 51%, and the Netherlands 37%.

5.2.1. National strategy and action plans

All three countries have NAPs in place. However, while Italy and Spain published new version of their plans in 2022, the Netherlands published their NAP in 2015 for the 2015-2019 period, and it has not been updated since.

5.2.1.1. National Action Plan structure

The structure of the NAPs is substantially different. The GAP proposed by the WHO in 2015 set five objectives: improve awareness and understanding, strengthen the knowledge and evidence base through surveillance and research, reduce the incidence of infection, optimise the use of antimicrobials, and develop the economic case for sustainable investment.[4]

In **Italy** the structure, as well as the NAP in general, is much more detailed compared to the other countries' NAPs.[17–20] The strategy puts inclusive and integrated governance at its centre. It is then divided into four horizontal areas that support their NAP, and three vertical pillars dedicated to the main interventions for the prevention and control of antibiotic resistance in humans, animals and the environment (Figure 8). These horizontal areas are training; information, communication and transparency; research, innovation and bioethics; and national and international cooperation. The vertical pillars are surveillance

and monitoring, infection prevention, and the proper use of antibiotics. From there, they describe the importance of each pillar and the situation in Italy, while offering information on the objective, the main actions, the actors involved, the estimated period of compliance, and the indicators to measure this compliance.

Spain's NAP is divided into six main categories (Figure 8): surveillance of antibiotic consumption and resistance to antibiotics, control of resistance to antibiotics, prevention of the need for antibiotics, research strategies, training, and communication and public awareness.[17] Most of these main lines are divided into human health and animal health. Later, the NAP discusses the environment on a separate section not included under the six main categories.

The **Dutch** NAP takes the form of a letter from the then Minister of Health to the Dutch Parliament.[19] This letter covers six sectors that are based and focussed on human health (Figure 8). The sectors are: the international aspect of AMR, healthcare, animals, food , environment, and science/industry. A separate section covers communication on AMR. Subsequently, it includes with an annex in which these pillars are further detailed, including the actors involved, the timeline, and the current status of the objective.[20]

Figure 8. National Action Plans general structure

5.2.1.2. National strategy and action plan evaluation

1. NATIONAL STRATEGY AND ACTION PLAN	IT	ES	NL
1.1. Development of national action plan (NAP)			
1.1.1. Existence of national action plan (NAP)	🟢	🟢	🟠
1.1.2. NAP written from a "One-Health" perspective and overarching all relevant sectors	🟢	🟢	🟢
1.1.3. NAP based on thorough situational analysis	🟢	🟠	🟢
1.1.4. Alignment with the overarching objectives and consistency with the guiding principles of WHO's Global Action Plan on AMR	🟢	🟢	🟢
1.1.5. High-level commitment including budget allocation	🟠	🟠	🟠
1.1.6. NAP publicly available	🟢	🟢	🟢
1.2. Strategic plan			
1.2.1. Clearly-outlined goals, objectives, priorities	🟢	🟢	🟢
1.3. Operational plan			
1.3.1. Clearly-outlined activities and interventions	🟢	🟢	🟢
1.3.2. Linked to other national action plans on related topics (e.g., healthcare-associated infections/IPC, EU-harmonised AMR monitoring in certain animals and foodstuffs) or specific disease areas (e.g., tuberculosis, HIV, STIs)	🟢	🟢	🟢
1.4. Monitoring and evaluation of NAP			
1.4.1. Performance indicators	🟢	🔴	🔴
1.4.2. Clearly-outlined targets and timelines	🟢	🔴	🟢
1.4.3. Periodic reviews of progress and impact	🟢	🔴	🔴
1.5. Preparedness/response planning for AMR			
1.5.1. Preparedness and response planning for outbreaks of highly resistant pathogens	🟢	🟠	🟠
1.5.2. Strategy to ensure availability of new and existing antimicrobial agents, including narrow spectrum antimicrobials	🔴	🟢	🟢
1.5.3. Policies/enforcement to address counterfeit products/illegal online sales	🔴	🔴	🔴

All three NAPs have been written from a "One Health" perspective and are in alignment and consistent with the overarching objectives and guiding principles of WHO's Global Action Plan on AMR. However, the NAPs have a primary focus on human and animal health, and less so on environmental aspects. Where environment is mentioned, it is mainly in the context of awareness and training. In addition, plant health is not explicitly mentioned in any of the three NAPs. In general, all NAPs are closely aligned with GAP objectives.

NAPs are supposed to be based on an evidence-based situational analysis, describing the problem based on data and results of previous actions, reflecting discussions with stakeholders, and involving a SWOT (strengths, weaknesses, opportunities and threats) analysis.[6] Even though all three countries included (parts of) a situational analysis, the level of detail varies significantly. Spain's NAP analysis is much more generic and is largely based on the revision of the previous NAP rather than the preferred situational analysis of the areas of intervention. The information on which the Netherlands' NAP is based is somewhat more detailed, but Italy conducted the most in-depth situational analysis.

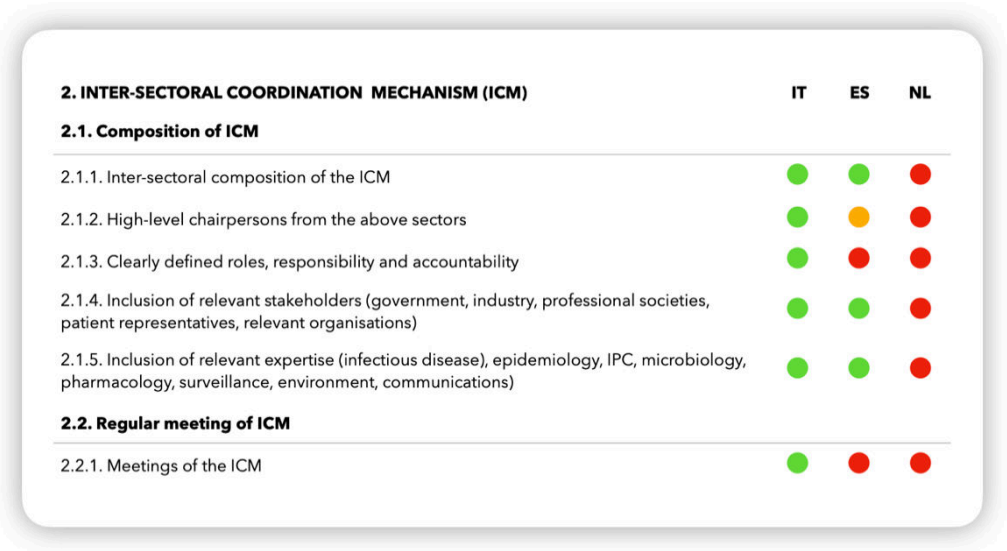
The high-level commitment to the NAPs requires timely approval, resourcing, sound transparent governance, and oversight. All NAPs were approved by a Minister or a high-level coordinator. However, none of the plans included an estimate of resources needed for multi-year budgetary provisions.

Goals and strategic objectives are clearly defined by all three countries, and many of the goals are intertwined with other plans that the countries are carrying out; mostly with plans for other communicable infections such as tuberculosis. However, there is a clear difference between the countries. Whereas Italy and the Netherlands show timelines and performance indicators to evaluate the progress of their plans, Spain has hardly any. Italy, presents the information in a very clear way, including the objectives, actions, actors, estimated term of completion and related indicators, at both the national and regional level in some cases.

Regarding outbreaks, Italy plans for them in the *surveillance of antibiotic resistance* section. They plan on a shared protocol for a rapid definition and notification of alert microorganisms (for example, microorganisms that are extremely/totally resistant to antibiotics) or events of particular importance (for example, outbreaks of multidrug resistant organisms). They also anticipate outbreaks in the *zoonosis prevention* section by establishing protocols, harmonised where possible, for early warning and management of possible epidemic conglomerates. Finally, they aim to develop a common protocol for early warning and management of possible epidemic outbreaks in this regard. In Spain, the section referring to outbreaks is also the *surveillance of antibiotic resistance*. They promote the use of the ADR *Surveillance Program* of the CNM-IS-CIII for the determination of emerging resistance mechanisms, molecular epidemiology and characterisation of outbreaks. They aim to integrate whole genome sequencing in the surveillance and study of outbreaks by multi-resistant microorganisms. However, there is no plan for managing these outbreaks.

The Netherlands plans on making sure there is an active monitoring and steering for AMS, prescribing behaviour, and policy *during outbreaks* as well as approved guidelines regarding outbreak management in nursing homes. Therefore, the Dutch plan is oriented on having information on the use of antibiotics during outbreaks and to ensure that there are proper guidelines to deal with outbreaks in nursing homes. However, they do not specify any other plan within the hospitals or in the community for the management of these outbreaks.

5.2.2. Inter-sectoral coordination mechanism



2. INTER-SECTORAL COORDINATION MECHANISM (ICM)	IT	ES	NL
2.1. Composition of ICM			
2.1.1. Inter-sectoral composition of the ICM	🟢	🟢	🔴
2.1.2. High-level chairpersons from the above sectors	🟢	🟡	🔴
2.1.3. Clearly defined roles, responsibility and accountability	🟢	🔴	🔴
2.1.4. Inclusion of relevant stakeholders (government, industry, professional societies, patient representatives, relevant organisations)	🟢	🟢	🔴
2.1.5. Inclusion of relevant expertise (infectious disease), epidemiology, IPC, microbiology, pharmacology, surveillance, environment, communications)	🟢	🟢	🔴
2.2. Regular meeting of ICM			
2.2.1. Meetings of the ICM	🟢	🔴	🔴

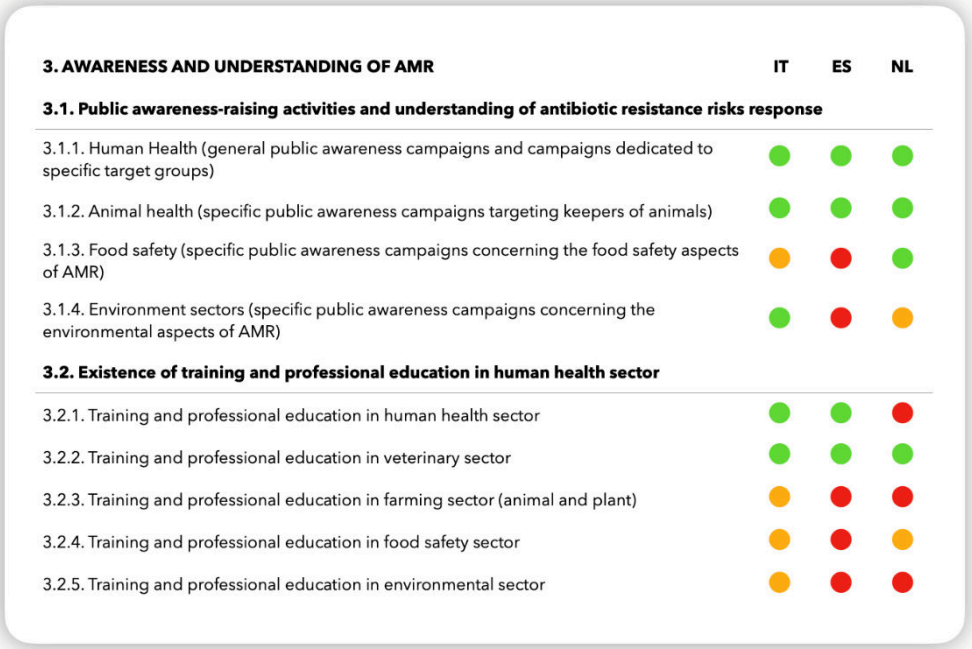
All three NAPs include, to some extent, references to an intersectoral coordination mechanism (ICM). However, the mandates of these structures are not clear, and the texts often lack detail on these structures or on which sectors are covered.

Italy specifically mentions an ICM, with the creation of the working group for the coordination of the national strategy against antimicrobial resistance (GTC-AMR). In addition, Italy has a section dedicated to governance in which they plan to define the specific responsibilities and coordination of the different national institutions in the governance of the NAP from a "One Health" perspective. They also guarantee the follow-up and updating of the NAP, as well as a mid-term and end-term evaluations that include possible proposals to update the national strategy. They included relevant stakeholders, such as the government, the pharmaceutical industry, or professional societies, and those with relevant expertise in infectious disease.

Spain interpreted the ICM as the people who coordinated the NAP; the Spanish Agency for Medicines and Health Products (AEMPS). Among the participants were several ministries, all the autonomous communities, 70 scientific societies, collegiate organisations, professional associations and universities, and more than 300 expert collaborators. However, the roles are not well defined, and it is not clear if there is a steering committee (such as in Italy) made up of various professionals, or what responsibilities the various actors will have in the implementation of the plan.

The Netherlands' NAP ICM lacks clarity. While it is clear that interdisciplinary collaboration happens, no mechanism or stakeholders are mentioned at all. In any case, it is understood that the main agency in charge of the NAP is The Minister of Health, Welfare and Sport. Moreover, the Annex mentions other government agencies, so they do include several government agencies. Therefore, there is some kind of intersectoral involvement, although its structure and responsibilities are not described.

5.2.3. Awareness and understanding of AMR



3. AWARENESS AND UNDERSTANDING OF AMR	IT	ES	NL
3.1. Public awareness-raising activities and understanding of antibiotic resistance risks response			
3.1.1. Human Health (general public awareness campaigns and campaigns dedicated to specific target groups)	🟢	🟢	🟢
3.1.2. Animal health (specific public awareness campaigns targeting keepers of animals)	🟢	🟢	🟢
3.1.3. Food safety (specific public awareness campaigns concerning the food safety aspects of AMR)	🟠	🔴	🟢
3.1.4. Environment sectors (specific public awareness campaigns concerning the environmental aspects of AMR)	🟢	🔴	🟠
3.2. Existence of training and professional education in human health sector			
3.2.1. Training and professional education in human health sector	🟢	🟢	🔴
3.2.2. Training and professional education in veterinary sector	🟢	🟢	🟢
3.2.3. Training and professional education in farming sector (animal and plant)	🟠	🔴	🔴
3.2.4. Training and professional education in food safety sector	🟠	🔴	🟠
3.2.5. Training and professional education in environmental sector	🟠	🔴	🔴

5.2.3.1. Public awareness-raising activities and understanding of antibiotic resistance risk response

Public awareness is important because of the poor understanding among the general population of the difference between viral and bacterial diseases, and how they are treated as well as the lack of importance of the One Health approach.[21] This topic, including targeting specific groups, is present in all NAPs. More specifically, most awareness campaigns focus on human health and antibiotic use reduction. This means animal health, food safety, and the environment do not take as much priority when it comes to awareness-raising activities. However, it is essential that citizens learn more about One Health and the intricate system of resistances. All sectors involved should be taken into account in awareness campaigns.[4]

Italy's first objective is the launch of a national integrated communication campaign on "*One Health*". Italy intends to create a strategy in which there are synergies between those involved in such a way that knowledge is cascaded through various channels. It also emphasises the importance of the transparency of the institutions. In addition, it takes into account raising awareness amongst journalists, media professionals and public communicators. They also aim to include the environment in their awareness activities, mainly targeting policy makers with this. However, most of their plans indicate "reaching all parties involved" and some of the examples they give are the general public, health- and veterinary professionals, and pharmacists, so it does not detail much if there are specific campaigns targeting other groups.

Spain divides this section into awareness raising campaigns, and visibility and dissemination of results. Its plan is mainly focussed on raising awareness about the importance of the prudent use of antibiotics by health professionals and the general public, as well as on the importance of adequate hand hygiene. It does have activities targeting veterinarians and the livestock sector but due to their characteristics, it is quite limited. Examples are posters on the prudent use of antibiotics that are available on a website, the development of informative articles, and answering requests for information. Spain also takes political decision-makers into account. Finally, Spain would set up a national survey to map the knowledge on antibiotic resistance to evaluate the activities developed.

The NAP describes the development and dissemination of educational information materials and resources from a One Health perspective for the general public and professionals. However, it is the only country out of the three that has a specific campaign on hygiene measures for preparation and storing of food in the kitchen. The Netherlands also aims to make administrators more aware of AMR.

5.2.3.2. Existence of training and professional education in human health sector

Training and professional education regarding AMR is also key to effective prevention. Italy intends to prepare a multidisciplinary elective teaching activity on AMR One Health topics. In addition, they aim to define a standard training program that includes ABR and AMR. Once again, Italy stands out here for not limiting their approach to human health, but instead acknowledging the AMR One Health approach. In addition, it includes a large number of University Degrees among its objectives, something that neither of the other two countries include. Next to that, they also include training activities for health and non-health professionals working in hospitals. Italy does not highlight the training of professionals through continuing educational courses as Spain does, focusing above all on future generations.

In the same way that Spain focusses on the importance of the prudent use of antibiotics in awareness raising, most of the training also shows this, mainly focusing on human health and the veterinary sector for professionals. Training in universities is also a big part of the plan but seems centred on the same topics.

Information on training and professional education is limited and does not specify the type of educational focus points per different professional group. Veterinarians are included mentioned as needing improvement via continuing education and peer review but there are no clear indicators on how to achieve that. In addition, education on general kitchen hygiene and AMR is also included.

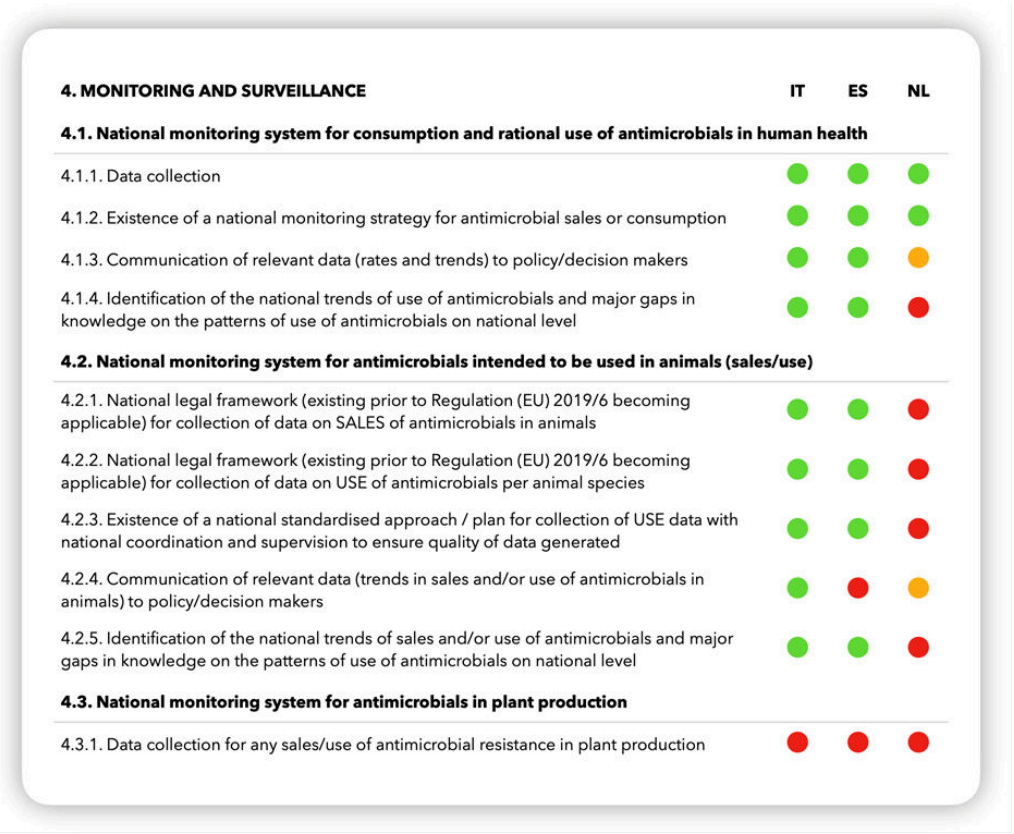
5.2.4. Monitoring and surveillance

National monitoring systems for the consumption and rational use of antimicrobials in human health, as well as monitoring for antimicrobials intended to be used in animals (sales/use), are in place in the three countries. Data on antibiotic resistance is sent to the European Antimicrobial Resistance Surveillance Network (EARS-Net), which is the largest publicly funded system for AMR surveillance in Europe. The monitoring of antibiotic consumption began in 2001 after the decision of the European Commission 2119/98/EC, initially through the coordination of the University of Antwerp in the context of the ESAC project (European Surveillance of Antibiotic Consumption), and subsequently through coordination of the ECDC in the context of the ESAC-Net network (European Surveillance of Antimicrobial Consumption Network).

Thanks to the web-based platform, known as TESSy (The European Surveillance System), ESAC-Net collects and historicises data, promoting its dissemination through the platform and annual reports.

In the veterinary sector, the main data source, until 2019, was sales data provided by the Marketing Authorisation Holders (MAs) within the European project ESVAC (The European Surveillance of Veterinary Antimicrobial Consumption), the results of which are reported in national reports on the sales of veterinary medicinal products containing antibiotic substances.

5.2.4.2. Antibiotic consumption



4. MONITORING AND SURVEILLANCE	IT	ES	NL
4.1. National monitoring system for consumption and rational use of antimicrobials in human health			
4.1.1. Data collection	🟢	🟢	🟢
4.1.2. Existence of a national monitoring strategy for antimicrobial sales or consumption	🟢	🟢	🟢
4.1.3. Communication of relevant data (rates and trends) to policy/decision makers	🟢	🟢	🟡
4.1.4. Identification of the national trends of use of antimicrobials and major gaps in knowledge on the patterns of use of antimicrobials on national level	🟢	🟢	🔴
4.2. National monitoring system for antimicrobials intended to be used in animals (sales/use)			
4.2.1. National legal framework (existing prior to Regulation (EU) 2019/6 becoming applicable) for collection of data on SALES of antimicrobials in animals	🟢	🟢	🔴
4.2.2. National legal framework (existing prior to Regulation (EU) 2019/6 becoming applicable) for collection of data on USE of antimicrobials per animal species	🟢	🟢	🔴
4.2.3. Existence of a national standardised approach / plan for collection of USE data with national coordination and supervision to ensure quality of data generated	🟢	🟢	🔴
4.2.4. Communication of relevant data (trends in sales and/or use of antimicrobials in animals) to policy/decision makers	🟢	🔴	🟡
4.2.5. Identification of the national trends of sales and/or use of antimicrobials and major gaps in knowledge on the patterns of use of antimicrobials on national level	🟢	🟢	🔴
4.3. National monitoring system for antimicrobials in plant production			
4.3.1. Data collection for any sales/use of antimicrobial resistance in plant production	🔴	🔴	🔴

Italy proposes an integrated surveillance model for the use of antibiotics in human and veterinary fields (One Health model) at a national level. To do so, they aim to develop a national report on the use of antibiotics in both human and veterinary fields to be correlated with antibiotic resistance data. Another action developed to reach their objective is the promotion of interoperability/national integration of the different information flows (e.g., pharmaceutical, electronic veterinary prescription, etc.) and new flows (e.g., computerised medical records, electronic health records) for monitoring the appropriateness at the local level, as well as at the hospital and veterinary level. They also plan to develop an integrated system shared between the veterinary health sector and the entity that collects various indicators and defines distinct reduction objectives for species and/or categories, as well as periodic analysis of the consumption of antibiotics (above a certain threshold) with consequent interventions, where necessary, including training and information.

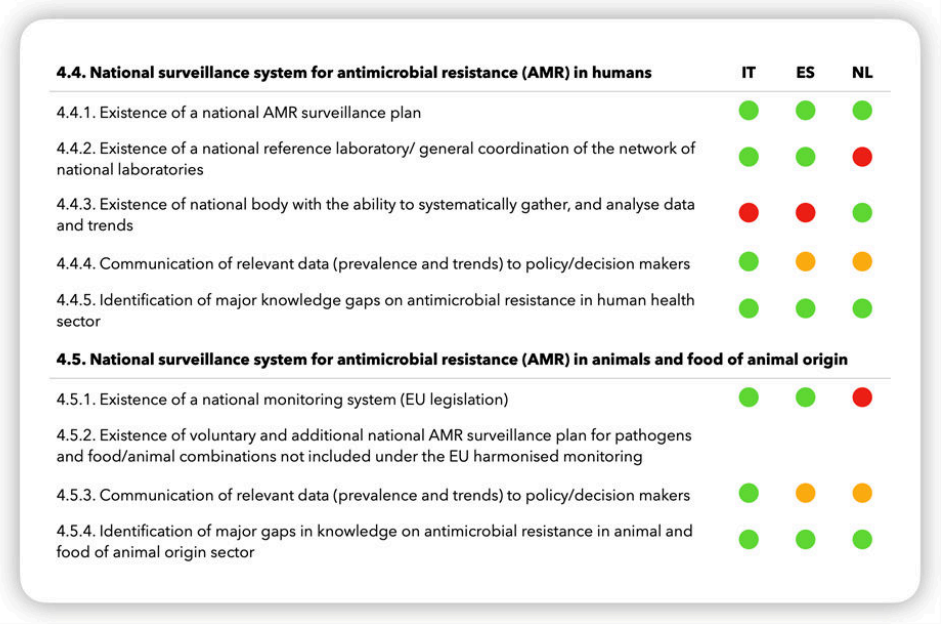
Finally, Italy aims to monitor the impact of their NAP on reducing the inappropriate consumption of antibiotics. Hence, since both human health and animal health surveillances are integrated, Italy does not divide this section in two and provide them from the One Health perspective.

Spain wants to agree on reduction targets of antibiotic consumption with the autonomous communities, as well as improve accessibility and improve dissemination of consumption data. They also plan to develop indicators that would allow a better understanding of the clinical and epidemiological situation of Spain, to promote actions that allow a disaggregated and homogeneous analysis of consumption data, as well as to improve the consultation tool based on the needs that are identified. In their NAP, Spain expands surveillance by including specific plans to include surveillance of antifungal and tuberculosis consumption, and implementation of hospital antibiotic consumption indicators in the NAP consumption tool.

Regarding animals, Spain aims to collect and compare data on sales and use of antimicrobials by species, in order to develop specific measures for the control and reasonable use of antimicrobials in veterinary medicine. They also want to identify relevant trends in sales volume and use of antimicrobials in animals. Further, the NAP aims to identify risk factors by monitoring the use of antimicrobials in animal and update the database of the ESVAC to adapt it to the requirements included in Regulations 2021/578 and 2022/209 for the collection of data on sales and use of antimicrobials. Finally, they want to establish indicators to be able to monitor the impact of the actions taken within the framework of the NAP to address antimicrobial resistance in the animal sector.

The Netherlands provides little information on antibiotic consumption data. Its NAP mentions that they want to make sure there is a uniform and reproducible view of antibiotic use in relation to the condition, and the status of infection prevention, in all healthcare networks, uniform and reproducible oversight of antibiotic use in relation to the disease, and the status of infection prevention should be ensured. However, little information is available on this. Very limited information is included on the monitoring within animals or plant production.

5.2.4.1. Antibiotic resistance in humans, animals and food of animal origin



4.4. National surveillance system for antimicrobial resistance (AMR) in humans	IT	ES	NL
4.4.1. Existence of a national AMR surveillance plan	●	●	●
4.4.2. Existence of a national reference laboratory/ general coordination of the network of national laboratories	●	●	●
4.4.3. Existence of national body with the ability to systematically gather, and analyse data and trends	●	●	●
4.4.4. Communication of relevant data (prevalence and trends) to policy/decision makers	●	●	●
4.4.5. Identification of major knowledge gaps on antimicrobial resistance in human health sector	●	●	●
4.5. National surveillance system for antimicrobial resistance (AMR) in animals and food of animal origin			
4.5.1. Existence of a national monitoring system (EU legislation)	●	●	●
4.5.2. Existence of voluntary and additional national AMR surveillance plan for pathogens and food/animal combinations not included under the EU harmonised monitoring			
4.5.3. Communication of relevant data (prevalence and trends) to policy/decision makers	●	●	●
4.5.4. Identification of major gaps in knowledge on antimicrobial resistance in animal and food of animal origin sector	●	●	●

National surveillance of AMR for human health in Italy is carried out through the Antibiotic-Resistance (AR-ISS) surveillance system, coordinated by the Istituto Superiore di Sanità (ISS). The national reference laboratory for surveillance is the National Reference Laboratory for Antimicrobial Resistance (NRL-AR). To strengthen surveillance, Italy plans on creating a network of regional reference laboratories for AMR and healthcare-acquired infections.

Italy also takes action in identifying knowledge gaps by assessing the need for new surveillance, as well as with specific studies for the surveillance of clinically and epidemiologically relevant pathogens and resistance mechanisms. They also aim to create a structured and regulated system for sharing data and information, from the local/regional to the national/European level and vice versa, following a One Health approach.

In the Italian veterinary sector, AMR monitoring activities in livestock and meat products have been implemented for some time.[a] The monitoring plan, issued annually by the Ministry of Health, is implemented by the Regions and Public Administrations and makes use of the collaboration of the NRL-AR and the National Reference Centre (CRN-AR) for data production and reporting. In contrast to farm animals, a representative and harmonised antibiotic resistance monitoring system has not yet been implemented in the EU for companion animals.

Italy, with the new NAP, plans to monitor AMR in pathogenic microorganisms of food and companion animals by developing guidelines on the requirements for performing antibiotic susceptibility testing for pathogenic bacteria. Further, they will carry out a census among the public and/or private laboratories that perform antibiotic susceptibility testing and create an application for the collection, management, and the consultation of antibiotic-resistance data produced by laboratories in the national territory. All these measures aim to reach pets as well as food producing animals. Finally, they aim to integrate AMR surveillance in humans and animals, as well as the evaluation of the connection between human strains and strains of animal origin.

[a.] As required by Decisions 2013/652/EU10 and 2020/1729/EU11

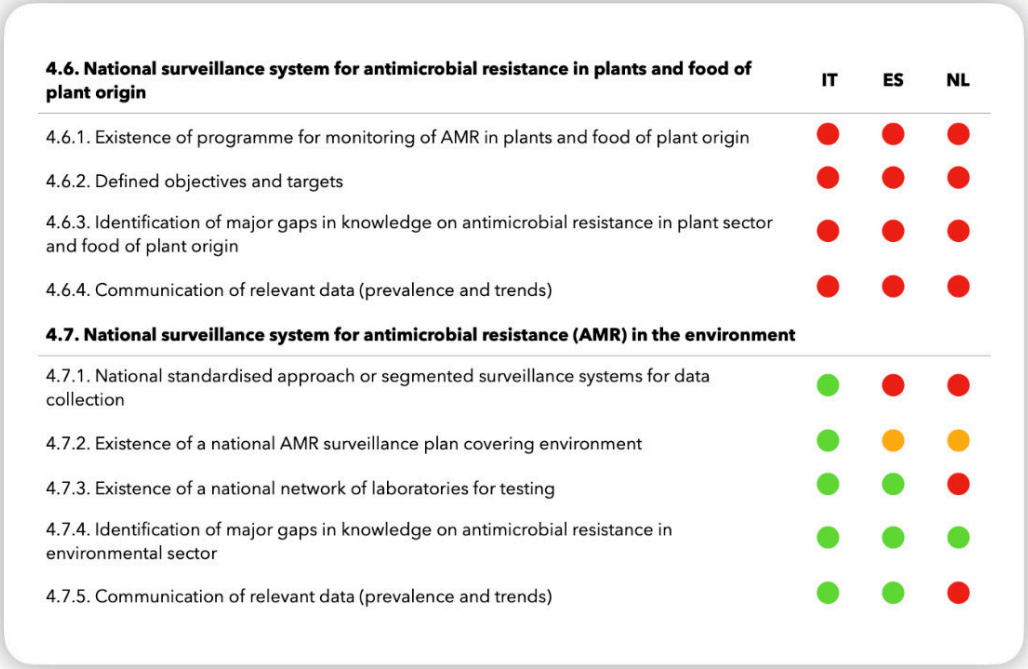
In its NAP, Spain plans to expand the surveillance of resistance to new antimicrobials, including antifungals and antituberculosis in human health, and antivirals and antiprotozoal in animal health. This is important because they do not only focus on ABR but AMR. Next to that, other microorganisms, such as resistant fungi or other microorganisms that arise from clinical relevance, will be controlled. For monitoring of resistance, the main goal of Spain is the implementation of the *National Antimicrobial Resistance Surveillance System* by including it in the Public Health legislation. Regarding animals, Spain intends to promote the development and consolidation of the *Clinical Pathogenic Bacteria Surveillance Project* in order to determine the AMR by species, monitor trends, and detect emerging AMR pathogens. Spain also shows commitment in identifying gaps in knowledge by assessing the risk of AMR transmission from animals to humans through non-food routes, for example, by direct contact with companion animals.

The Netherlands includes goals for their EU Presidency of 2016, as well as many international commitments regarding AMR surveillance, such as countries receiving information on and assistance with surveillance through the National Institute for Public Health and the Environment (RIVM), appointed as WHO Collaborating Centre for Antimicrobial Resistance Epidemiology and Surveillance; improving surveillance through representation, and the active contribution of the RIVM in various international networks regarding surveillance of antibiotic resistance and healthcare-acquired infections. The reference to the Dutch EU Presidency highlights the need for an updated plan; the Dutch EU Presidency was seven years ago.

The Netherlands also has some specific national actions on surveillance in their plan. They plan to introduce the requirement that every healthcare facility has a protocol for surveillance of multidrug resistance, and that AMR-related data should be accessible to all stakeholders. The Dutch NAP also wants to ensure involvement of stakeholders in and governance of the surveillance system. Moreover, they plan on making resistance information more transparent and accessible by ensuring information is accessible between healthcare facilities, regional Public Health Services (GGDs), as well as other healthcare providers and laboratory specialists. However, the Dutch plan does not include any information on surveillance of AMR in animals and food of animal origin.

Plant health is not explicitly mentioned in One Health NAPs. According to the *Member States' One Health National Action Plans against Antimicrobial Resistance Overview report*, prepared by the DG Health and Food Safety, most Member States report surveillance activities in this sector in their reply to the Global Database for Tracking Antimicrobial Resistance (AMR) Country Self- Assessment Survey (TrACSS). The main reasons provided for not including plant health in their NAPs are that plant protection products are mostly covered under specific EU legislation, that antibiotics are not authorised for this purpose, or that this sector was excluded from the NAPs following a prioritising exercise. However, these considerations are not explained in the NAPs (e.g., in the situational analysis).[6]

5.2.4.1.1. Antibiotic resistance in the environment



4.6. National surveillance system for antimicrobial resistance in plants and food of plant origin	IT	ES	NL
4.6.1. Existence of programme for monitoring of AMR in plants and food of plant origin	🔴	🔴	🔴
4.6.2. Defined objectives and targets	🔴	🔴	🔴
4.6.3. Identification of major gaps in knowledge on antimicrobial resistance in plant sector and food of plant origin	🔴	🔴	🔴
4.6.4. Communication of relevant data (prevalence and trends)	🔴	🔴	🔴
4.7. National surveillance system for antimicrobial resistance (AMR) in the environment			
4.7.1. National standardised approach or segmented surveillance systems for data collection	🟢	🔴	🔴
4.7.2. Existence of a national AMR surveillance plan covering environment	🟢	🟡	🟡
4.7.3. Existence of a national network of laboratories for testing	🟢	🟢	🔴
4.7.4. Identification of major gaps in knowledge on antimicrobial resistance in environmental sector	🟢	🟢	🟢
4.7.5. Communication of relevant data (prevalence and trends)	🟢	🟢	🔴

Environmental surveillance plans vary greatly from country to country. As, in general, the initiatives related to the environment are few, they will be summarised in this section despite the fact that they do not correspond solely to monitoring. Nevertheless, **Italy** is the only country with an explicit plan on environmental monitoring of antibiotics and antibiotic resistance. However, it is very focused on monitoring the presence of antimicrobials in the water. To increase the level of knowledge on the presence of antibiotics in aquatic environments, three separate but complementary actions are proposed.

Research for antibiotics and resistance genes through the strengthening of the national surface water monitoring network is managed by the National Network System for the Protection of Environment (SNPA), which is already operating in the monitoring of the concentrations of the five antibiotics envisaged by the Watch List of the Water Framework Directive. The Watch List could be further improved adding highly toxic substances that are used in many Member States and released into the aquatic environment, but rarely or never monitored. For their first objective they aim to create and progressively develop a network for *environmental monitoring* of the most relevant antibiotic substances (in particular antibiotics for resistant bacteria) and of the genes of resistance in the environment, organising a network starting from the SNPA laboratories and in close coordination with the "Environmental Health Biodiversity and Climate" Project of the National Coverage and Resilience Plan.

Further, research will also be by means of monitoring the sewage system through the strengthening of the centres belonging to the nascent SARS-CoV-2 monitoring network and extending their competences to ABR. Therefore, the integration of routine surveillance of SARS-CoV-2 will be further improved with the integration of antibiotic research, resistant bacteria and resistance genes. Finally, to ensure the expansion of knowledge in terms of emissions into the environment of antibiotic substances, pathogens and resistance genes they plan on launching a survey on the characteristics of the most

significant discharges deriving from companies producing these substances. To this end, agreements and protocols would be activated with the main producers' associations to launch waste characterisation programmes and encourage the implementation of the best techniques available for prevention at the source and for the complete abatement of these substances in the treatment plants.

As for **Spain**, it has an environmental plan that consists of three phases. The *first phase* is the identification of the emission points of resistance determinants to the environment and in the characterisation of the environmental behaviour of the most widely used antibiotics. The *second* is the study of the existing environmental monitoring data and possible improvements of the monitoring plans, and the *third* is the study of risk analysis methodologies and possible impact on public and animal health of resistance in the environment. Quite exhaustive documents have emerged from the first and second phase. However, they are a research work rather than a monitoring system. Spain undoubtedly shows commitment to the investigation of antibiotics in the environment but does not reflect in its NAP the ways of obtaining data on environmental resistance. However, their NAP does include identifying where and when to take environmental samples to control the presence of antibiotics and AMR in the environment, as well completing phase 1 and 2 and starting phase 3 which would help to understand the problem, know the existing data and likely help create a good monitoring system.

In their NAP **the Netherlands** plan to contribute to a safer environment and thus reduce the import of resistance internationally. They also show commitment to the environment when planning on animal health, since while developing a new policy, attention will also be given to the effect of antibiotic use in animals on the environment. In addition, the Netherlands also has more explicit actions regarding the environment. The Netherlands Organisation for Health Research and Development (ZonMW) and the RIVM drafted a knowledge outline and policy recommendations regarding antibiotic resistance in the environment. This revealed that a great deal of national and international research has been conducted, but that results are difficult to compare due to the use of different criteria and quality requirements. This research showed that the environment does play a role in the transmission of antibiotic resistance. Therefore, the Netherlands asked the RIVM to draft an action plan for gaining better insight into the situation in the Netherlands. According to the NAP, where necessary, the RIVM will involve other actors (e.g., veterinary institutions/experts). The implementation of the NAP would need to be encompassed by measurement of the occurrence of resistant bacteria and the presence of (traces of) antibiotics in the environment. And therefore, measurements will also be performed in *wastewater* from health facilities and residential areas, in wastewater treatment plants and in manure, among other places. Therefore, the Netherlands also considers that the measurement of resistances in the environment should be performed mainly in water, similar to what the Italian plan suggests. However, the Netherlands does not specify whether water measurement will be something specific for the development of the plan or whether it will be actively monitored, becoming the central axis of monitoring in its plan. ABR will also be included in a number of initiatives, such as the “Green Deal Sustainable Operations in Healthcare” and in the new *water quality* policy. This deal involves 84 individual healthcare institutions through the 'environmental platform for healthcare’ and will also involve umbrella organisations such as the Dutch Hospitals Union (NVZ) and elderly care trade association, Actiz.

They also plan on implementing an action plan to advise on management measures and inputting *issues* into water quality policy. Lastly, they include some considerations through innovation by exploring entry points for preventive policies in healthcare and the environment.

5.2.4.3. Other considerations

The Netherlands does have some surveillance plans regarding food. Their NAP has two specific actions; one at the global level (Codex Alimentarius), in which want to push for intensive and harmonised monitoring for resistant bacteria, and another one for at the European level, pushing for a harmonised monitoring of resistant bacteria on meat imported from third countries.

Finally, Italy refers to plans in its NAP to adapt surveillance systems that are already in place for the monitoring of COVID-19.

5.2.5. Strengthening infection and prevention and control measures

5. STRENGTHEN INFECTION AND PREVENTION AND CONTROL MEASURES	IT	ES	NL
5.1. Human healthcare Infection Prevention and Control (IPC) measures			
5.1.1. Existence of IPC programmes at national level including national IPC guidelines	🟢	🔴	🟠
5.1.2. Education and training for IPC professionals	🟢	🟠	🟢
5.1.3. Monitoring and audits of IPC practices	🟢	🟢	🟢
5.2. Animal Health - Infection Prevention and Control (IPC)			
5.2.1. Policies and national legislation includes prevention measures in livestock, aquaculture [and pets]	🟢	🔴	🔴
5.2.2. Existence of initiatives to encourage/incentivise livestock keepers to have a farm health plan, as part of an integrated approach to on-farm animal health	🟠	🔴	🔴
5.2.3. National control and eradication programmes of specific animal diseases, other than those under EU Legislation	🔴	🔴	🔴

Infection prevention and control (IPC) is a practical, evidence-based approach preventing people and animals from being harmed by avoidable infections (WHO). For this part of the evaluation, this section is divided into two: human health and animal health IPC measures.

5.2.5.1. IPC measures in human health

Italy plans to prepare a National Plan for IPC of healthcare-acquired infections for all the regions, as well as to provide continuity in actions to support, update and monitor. In order to ensure the implementation, they propose additional actions. Meanwhile, Spain proposes measures that are part of the recommendations and programmes to reduce the risk of infection and transmission of AMR in hospitals and in primary care centres. Examples of programmes are hand hygiene, the “Zero Project”, the programme for the IPC of phlebitis associated with peripheral venous catheter, and the promotion of the use of sensitivity tests using European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. The Netherlands gives priority to ensuring that all hospitals and nursing homes have active infection prevention policies, and that any guideline on hygiene/infection prevention or careful antibiotic use and resistant bacteria is provided through patient information. However, the NAP does not indicate how this is to be implemented.

Regarding education and training, Italy aims to create a repository for the dissemination of documentaries, training and information materials on the topic. They also propose a training plan for healthcare-acquired infections intended for all healthcare and non-healthcare workers, including social and healthcare workers of hospitals. Spain does not explicitly mention many IPC training programmes, with the hand hygiene programme being the only exception. The aim of this programme is to promote and train health professionals in all healthcare areas of the National Health System (NHS), including the socio-health field, as well as to support WHO initiatives regarding IPC. Finally, the Netherlands includes that they want to achieve a good level of knowledge on infection prevention and antibiotic resistance of doctors, nurses, caregivers and paramedics through, amongst other measures, training.

The only country that explicitly mentions monitoring and auditing for IPC is Italy, where the NAP aims to develop a monitoring and accreditation system to ensure and recognise IPC practices. Spain focuses on monitoring by completing the implementation of the healthcare acquired infections surveillance system with its existing five modules: surgical site infection, healthcare-acquired infection prevalence in hospitals and in intensive care units (ICUs), monitoring multidrug-resistant bacteria, and outbreaks in the regions. In addition, they plan on including healthcare-acquired infections surveillance in the Royal Decree on Public Health. The Netherlands includes the development of a surveillance system of antibiotic use in relation to the disease, and the status of infection prevention in all healthcare networks that is uniform and reproducible, to which all healthcare providers provide data.

It is worth mentioning the different points of view that Italy and the Netherlands include in their plan. One of the measures with which Italy hopes to reduce infections, and therefore boost IPC, is through vaccinations. Hence, their plan includes actions to ensure enough vaccination coverage in the general population and in groups at risk. The Netherlands however advocates for innovation. To promote the development of innovations in infection prevention, they propose a new ZonMw antibiotic resistance programme and name some examples, such as urinary catheters with antimicrobial coatings or mobile inflatable airlocks for isolation rooms.

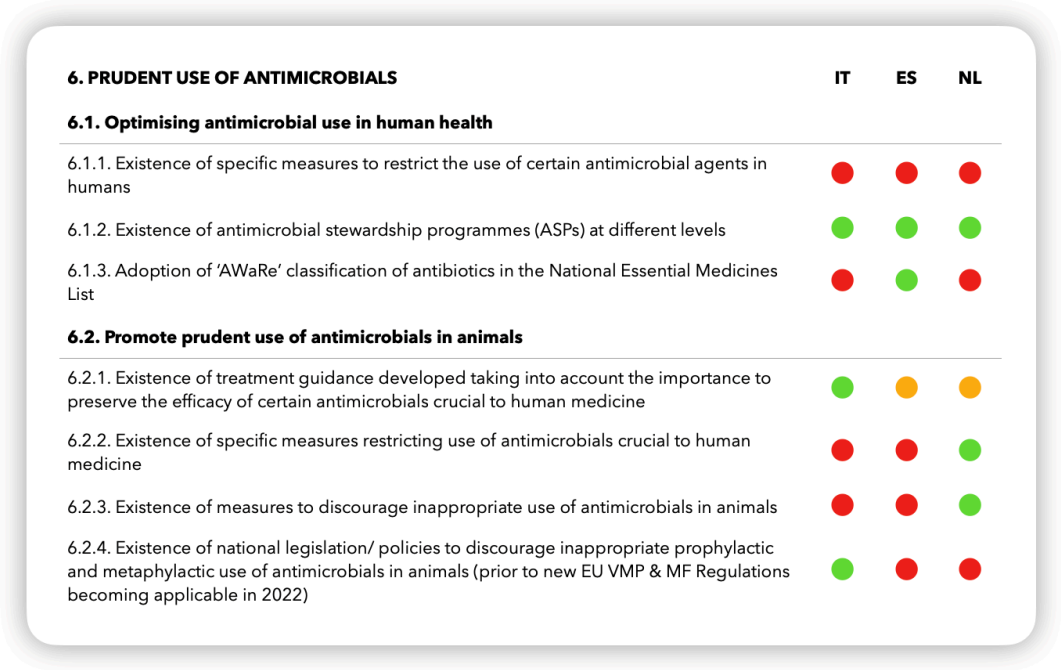
5.2.5.2. IPC in animals

Italy aims to reduce zoonotic infections by strengthening the knowledge on the main zoonotic microorganisms and improving integration in the human and veterinary sectors. They will promote the adoption of appropriate measures to prevent communicable diseases (“zoonoses”) by supporting the adoption of vaccination protocols, prophylaxis, the protection of biodiversity as a preventive factor against spill-over, and the evaluation of the health status of animals and therefore of the breeding (stewardship) through the evaluation of the ABMs (Animal-Based Measures). They also aim to strengthen knowledge on emerging diseases, potentially zoonotic diseases, which can have serious consequences for public health, animal health and biodiversity. In order to promote the protection of biodiversity, they aim to insert the specific theme in rural development policies (CAP). This implies Italy wants farmers and other animal handlers to have a health plan, in addition to all the work related to the administration of vaccines previously described. Italy plans to economically compensate operators to support improvements in aspects of well-being, biosecurity, and reduction of antibiotic consumption in animals.

Spain's NAP focus is mainly on the prudent use of antibiotics, but few plans on animal health and zoonoses are mentioned. The Netherlands' NAP plans on animal disease prevention by supporting research into improving the health of livestock. They also want to improve general animal health in order to achieve extremely restricted antibiotic use while acknowledging the challenge this poses for the actors involved. Therefore, they aim to ensure that restricted and prudent antibiotic use is linked to innovation and sustainability agendas of all the chains affected.

5.2.6. Prudent use of antimicrobials

This sector also has two main facets, human health and animal health.



6. PRUDENT USE OF ANTIMICROBIALS	IT	ES	NL
6.1. Optimising antimicrobial use in human health			
6.1.1. Existence of specific measures to restrict the use of certain antimicrobial agents in humans	🔴	🔴	🔴
6.1.2. Existence of antimicrobial stewardship programmes (ASPs) at different levels	🟢	🟢	🟢
6.1.3. Adoption of 'AWaRe' classification of antibiotics in the National Essential Medicines List	🔴	🟢	🔴
6.2. Promote prudent use of antimicrobials in animals			
6.2.1. Existence of treatment guidance developed taking into account the importance to preserve the efficacy of certain antimicrobials crucial to human medicine	🟢	🟠	🟠
6.2.2. Existence of specific measures restricting use of antimicrobials crucial to human medicine	🔴	🔴	🟢
6.2.3. Existence of measures to discourage inappropriate use of antimicrobials in animals	🔴	🔴	🟢
6.2.4. Existence of national legislation/ policies to discourage inappropriate prophylactic and metaphylactic use of antimicrobials in animals (prior to new EU VMP & MF Regulations becoming applicable in 2022)	🟢	🔴	🔴

5.2.6.1. Optimising antimicrobial use in human health

Italy mainly aims to provide operational indications on the implementation of actions aimed to improve the appropriateness of prescription and of use in the hospital and community fields. In order to do so, they will develop a new structure for a model of antimicrobial stewardship (AMS). This model of AMS would define operating standards, priority activities, process and result indicators. It will also identify priority areas for national recommendations and/or guidelines on the appropriate use of antibiotics and promote and disseminate the interventions in clinical practice to support the appropriate prescription of antibiotics.

Spain includes many of the actions for the prudent use of antibiotics in their plan for control of antibiotic resistance. Spain's AMS program is mainly based on the Antibiotic Use Optimization Programmes / Teams (known as PROA). They aim to improve its implementation in hospital and health areas of the NHS. With this strategy based on PROAs, they also want to complete the development of PROA computer tools, also known as the WASPSS (Wise Antimicrobial Stewardship Support System) project, in order to ensure better antibiotic use. They also plan on using RAVARA (a registry of antimicrobial use of high strategic value and recently approved) to understand the real conditions of high strategic value antibiotics. This will facilitate their monitoring and obtain information on

their use to assess their inclusion in specific use programs. Other actions to optimise antimicrobial use are prescription support through a national implementation of an out-of-hospital prescription support system, and the adaptation of the format of the antibiotic containers. Spain is also the only country that mention the adaptation of the WHO AW*aRe* strategy to local resistance and national authorisations in its plan.

One of the objectives in the Netherlands NAP is to make sure that each healthcare facility establishes who is responsible for implementing and coordinating AMS programmes, including implementing guidelines and standards. They also plan on active monitoring and AMS, prescribing behaviour, and policies during outbreaks. The *Health Care Inspectorate* (IGZ) is responsible for the monitoring. As previously described, they want to make sure there is a uniform and reproducible view on antibiotic use in relation to the disease so information on the use of antibiotics will be more transparent. At the international level, plans include the development of a roadmap by RIVM and WHO EURO that would support countries in the development of tailored interventions on prudent antimicrobial use (Guide to Tailoring AMR Programmes - TAP), or a plan to address gaps in the global agenda on the development and proper use of new resources.

5.2.6.2. The promotion of prudent use of antimicrobials in animals

Italy plans to reduce of the use of antimicrobials for metaphylaxis and prophylaxis in food-producing animals. They also mention actions such as issuing a legislative decree containing measures to combat antimicrobial resistance, and review of national and sector guidelines (dairy cattle, pigs and rabbits) on the rational use of antibiotics in the livestock sector, with specific recommendations for the limited use of antibiotics for metaphylactic and prophylactic treatments. They further plan on giving economic support to operators to support improvements in aspects of well-being, biosecurity and reduction of antibiotic consumption. Italy's plan also aims to strengthen the prudent use of antibiotics in food-producing and companion animals with multiple actions, such as establishing industry guidelines on the prudent use of antibiotics for species of relevance (poultry, veal calves and bullocks, aquaculture). Finally, they will be monitoring the prescriptions of medicines containing HPCIAs (Highest Priority – Critically Important Antibiotics) (veterinary and human) outside the terms of the MA, keeping in mind the "One Health" perspective, allowing them to determine if the prudent use of these antibiotics is taking place.

Spain has multiple initiatives to promote the prudent use of antibiotics in animals. One of them is called "Reduce", which includes programmes for the prudent use of antibiotics and the *voluntary* reduction of the consumption of certain antibiotics in different species. Their plan aims to create new "Reduce" projects and expand them to other species. In addition, in 2022 Spain published a Royal Decree establishing the framework for action to achieve sustainable use of antibiotics in livestock species. With this in mind, they want to define a reference indicator that will be taken as the maximum value of annual consumption, which will be calculated at the farm level. The adequacy of the format of the antimicrobial containers in relation to the proposed route of administration and the dosage and the species(s) of destiny is another initiative. In addition, they developed and promote the widespread use of the "Antimicrobial Prescribing Guides: One Health" in both humans and animals. The last project conducted by a working group aims to improve the availability of veterinary drugs and alternatives to the use of antimicrobials. It aims to promote the development and introduction of new veterinary drugs on the market, or the availability of existing ones in other species, and updating veterinary drugs to adapt to the new veterinary legislation (NLV).

Internationally, the Netherlands plans on contributing to the implementation of the WHO antimicrobial resistance Global Action Plan and other international guidelines. Via this international partnership, they seek to motivate their partners to reduce antibiotic resistance in animal farming within their countries based on their precautionary principle and the practice of reducing antibiotic usage in animal farming.

The Netherlands set its goal in the reduction and prudent use of antibiotics in animal farming in order to limit the development of resistance where possible. In order to do so, they plan on implementing additional measures by sectors and veterinarians. They aim to encourage farmers and veterinarians to shift towards the 'target area' of restrained and prudent antibiotic use. Other initiatives are the prudent and restricted use in other animal sectors (pets, horses, rabbits, etc.) along with reduction of critical antibiotic use in these sectors. To this end, the NAP formulates the following activities: the continuation of more stringent the Netherlands Food and Consumer Product Safety Authority (NVWA) inspections; enforcement of restricted antibiotic use in animal farming; identification and control of illegal activities; and the improvement of general animal health in order to achieve extremely restricted antibiotic use. In addition, they want restricted and prudent antibiotic use to be linked to the innovation and sustainability agendas of all the chains affected.

5.2.7. Investment/research programmes in the area of AMR

7. INVESTMENT/RESEARCH PROGRAMMES IN THE AREA OF AMR	IT	ES	NL
7.1. Investment/research programmes in the area of AMR			
7.1.1. Investment/research programmes to support the development of new medicines, diagnostic tools and vaccines (national)	●	●	●
7.1.2. Investment/ research programmes in other areas	●	●	●
7.1.3. International collaborative work on research or other areas linked to AMR	●	●	●

Italy wants to encourage cross-sectional, collaborative and interdisciplinary research in the field of antibiotic resistance with a One Health approach. They propose this with specific actions, such as the dissemination of the results of the programmes of antimicrobial resistance financed within the scope of the Health Ministry (MdS) and of the independent financial research from the Italian drug agency (AIFA), of the National Centre for Disease Prevention and Control (CCM), and of the Ministry of University and Research (MUR). They also want to support research of alternatives to antimicrobials and of new vaccines, especially those directed against microorganisms critical to ABR, and encourage their use after authorisation.

Spain's investment and research programmes often lack concrete actions that exactly indicate the magnitude of the projects. They aim to have a *Common Strategy in Resistance Research* and, to achieve it, some of the actions they mention are to increase financing, participation and success of Spanish groups in the calls of the Joint Programming Initiative-AMR (JPI-AMR).

They also aim to promote cooperative research initiatives from the Antimicrobial Resistance Programme of Spain's Infectious Diseases Network Research Centre. They further aim to promote projects developed by the Database for Pharma-epidemiological Research in Primary Care (BIFAP) of the AEMPS, as well as disseminate reports of joint inter-agency antimicrobial consumption and resistance analysis (JIACRA).

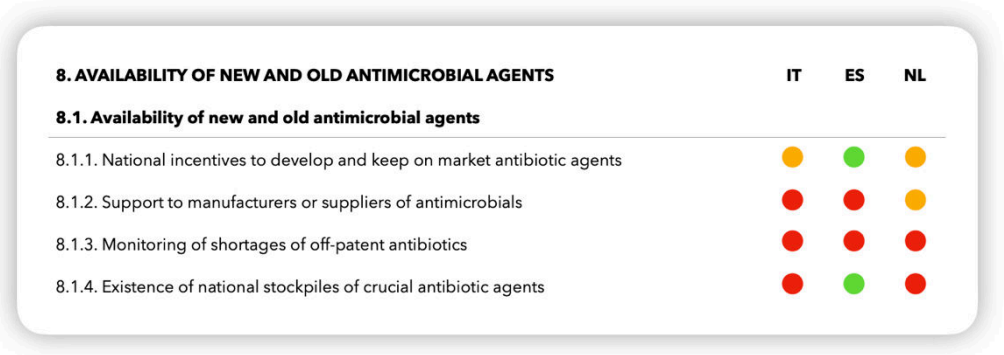
Spain also aims to incentivise the development of new antimicrobial treatments. Its specific objectives are to understand and adapt the regulatory and financing actions and strategies agreed with the European countries, to establish a framework for dialogue with all the agents involved in the development of new antibiotics and alternatives and to develop targeted proposals to improve national and European access routes to new antibiotics.

With its NAP, the Netherlands wants to promote the development of new antibiotics, diagnostics and treatments, including alternatives to antibiotics, by strengthening research infrastructure, and by bringing together and sharing knowledge and input from results in public-private partnerships. They also aim to financially and substantively support WHO in strengthening global cooperation for development of new business models in the framework of the GAP on AMR. Actions include promoting the development of new business models for antibiotic development in international initiatives and a better cooperation between EU Member States on the area of research (alignment, joint programming and funding) through participation in JPI antibiotic resistance.

In addition, the Netherlands proposes a fairly broad set of measures in its research strategy. They aim to support and cooperate in international initiatives designed to develop new business models. They also plan to identify the main bottlenecks in development and marketing authorisation process and to facilitate the acceleration of clinical research with and the authorisation process for new antibiotics. In addition, they propose two international initiatives: to support the development of international fundamental scientific knowledge by commissioning a new assignment to The Netherlands Organisation for Health Research and Development (ZonMW) and to support permanent participation in the European JPI on antimicrobial resistance.

The Netherlands believes that in addition to the development of new medicines, there are also gains to be achieved by new initiatives regarding alternative treatments, infection prevention, and countering spread. Therefore, they expect that through the 'quality programme in long- term care' and the 'experimental article' (a temporary article intended to evaluate the results of implementing new policy), it will promote the development of some of these innovations.

5.2.8. Availability of new and old antimicrobial agents



8. AVAILABILITY OF NEW AND OLD ANTIMICROBIAL AGENTS	IT	ES	NL
8.1. Availability of new and old antimicrobial agents			
8.1.1. National incentives to develop and keep on market antibiotic agents	🟡	🟢	🟡
8.1.2. Support to manufacturers or suppliers of antimicrobials	🔴	🔴	🟡
8.1.3. Monitoring of shortages of off-patent antibiotics	🔴	🔴	🔴
8.1.4. Existence of national stockpiles of crucial antibiotic agents	🔴	🟢	🔴

Italy has a different approach to the strategy against AMR; based on looking for alternatives (partly as the Netherlands does), such as vaccination, more so than on the development of new antibiotics. In their own words: “It should be noted that ABR is inevitable when only antibiotics are used and that continuous production of new antibiotics that may be effective against resistant microorganisms is necessary. However, vaccination represents a more sustainable approach that can be used for decades without generating significant resistance”.

Therefore, under innovation they propose research on different topics. Some of these are therapy of multi-resistant bacterial agents; design, synthesis and construction of libraries of molecules to be tested against multi-resistant bacterial agents and “early stage” translational research models to establish “proof-of-concept” of new and non-traditional drugs that provide treatment alternatives for patients with multidrug resistant germ infections.

In addition, Italy offers a long list of technological innovations that could be applied to the development of antibiotics or alternatives such as chemical modification of existing antimicrobials, design of chimeric antimicrobial agents or by applying anti-biofilm strategies. Therefore, this strategy does not only apply to antimicrobials but also non-traditional treatment options such as monoclonal antibodies, bacteriophages, antimicrobial peptides, "resistance breakers", "antibacterial enhancers" and virulence attenuators. For this reason, Italy does not stand out in this section since it does not have much planned for the availability of new and old antibiotics.

What best fits the description within the Spanish plan of old antibiotics is what they call *the Antibiotics of Special Clinical Relevance*; which are generally older, less selective and don’t involve new resistance mechanisms. In their plan they aim to promote access to these antibiotics to prevent the appearance of new ADRs and control existing ones. To do so, they propose regulatory measures to guarantee the correct supply of all pharmaceutical forms and necessary doses of antibiotics considered critical. Regarding newer antibiotics, they plan on incentives for the development of new antimicrobial treatments. To do so, they aim to adapt and implement the regulatory and financial actions and strategies agreed with European countries.

Hence, Spain's strategy is passive, letting its action depend on European consensus. In addition, they aim to create a framework for dialogue with all the agents involved in the development of new antibiotics and alternatives to develop proposals aimed at improving national and European access routes to new antibiotics.

The *innovation* section of the Dutch plan proposes promoting the development of new antibiotics, diagnostics and new treatments, including alternatives to antibiotics. They want to do this by strengthening research infrastructure, bringing together and sharing knowledge and input from results in PPPs based on knowledge agenda. They also aim to accelerate the antibiotic registration process by identifying and resolving bottlenecks in the regulatory process. This includes mapping the bottlenecks and opportunities/white spots around the development of new antibiotics and alternatives. They also want to promote development of new business models for antibiotic development in international initiatives.

Internationally, they want to promote research on new resources and good use, through; encouraging participation in contributions to Horizon2020 (EU wide research programme) and the Innovative Medicines Initiative (PPP programme), and promote participation in JPI antibiotic resistance by other (non-EU) States.

6. DISCUSSION

6.1. From an Epidemiological Perspective

Antimicrobial Resistance Rates

Italy, Spain and the Netherlands have very different epidemiological situations and therefore the challenges they face also differ. However, AMR has increased in all three countries, with the increase being most prominent in Italy and Spain. All three countries must therefore continue to ramp up efforts to prevent the current increase in AMR. Italy and Spain have a clear advantage over the Netherlands, as reducing their use of antibiotics, which is at the moment much higher compared to the Netherlands, could already garner significant benefits.

Antibiotic Consumption Rates

The consumption of antibiotics, as well as the sale of veterinary antibiotics, is clearly higher in Italy and Spain than in the Netherlands. Italy must continue its efforts to ensure the downwards trend in its antibiotic consumption rate that has been seen over the last few years, while Spain should strengthen their efforts to recover the downward trend that was observed from 2016 to 2020. Further, the high use of penicillin stands out in Spain and Italy compared to the Netherlands. Targeted strategies to reduce the use of these antibiotics in the community in both countries may considerably improve AMR rates, since antibiotic consumption has been directly related to AMR rates.[24] For this reason, countries should give more importance to AMS programmes in their NAPs. Regarding the sale of antibiotics for veterinary use, the countries should continue their efforts to ensure continuation of the observed positive trends in reductions of sales. A relatively easy way to reduce antibiotic use is to target non-therapeutic antibiotic usage.[25]

Healthcare-Acquired Infections

Data on healthcare-acquired infections are hard to come by, though the ECDC estimates that there are three million cases yearly.[26] The EU obtains data from specific programmes such as healthcare-acquired infections in long-term care facilities, in intensive care units,

and surgical sites. However, data on healthcare-acquired infections in acute care hospitals are collected only sporadically[16], while they would provide valuable information on other routes of hospital infections that could facilitate the development of better IPC strategies in hospitals. In addition, these measures have proven to be one of the most important strategies, together with the reduction of antimicrobial use, in the fight against resistance. This is especially useful because about 50% of healthcare-acquired infections are preventable.[27]

Antibiotic Resistance vs Antimicrobial Resistance

Most of the information that is collected is about bacterial infections and antibiotics. However, it is imperative that resistance information from microorganisms other than bacteria is integrated, and that more information on antimicrobials is included, instead of focusing exclusively on antibiotics. Even though some NAPs, such as the Spanish one, do mention other related plans, such as the NAP on tuberculosis, the NAPs have a clear focus on antibacterial resistance.

6.2. National Action Plans

6.2.1. National strategy and action plan

The need for a similar basis on which to structure plans

Italy, Spain and the Netherlands present radically different plans with very different structures. The main focus point of the three plans is also very different: in Italy it is governance, in Spain there is a more linear structure in which they give great importance to the previous NAP, and in the Netherlands the focus is on human health. This makes the priorities of the three plans very different, making objective comparisons of the three countries difficult. Next to that, some studies suggest that variance in NAPs also leads to variance in implementation of AMR policy.[28] Therefore, requiring NAPs to follow a similar structure, with the One Health principle as the core of their NAPs, would allow for easier comparison and facilitate best-practices learning. The EU could use the variety in countries' NAPs to identify best practices and come up with a guideline for these plans. Efforts have already been undertaken to establish a governance framework that would enhance the successful execution of NAPs.[29] The EU should draw inspiration from this approach.

The need for more detailed information in NAPs

The EU tool applied for this research was previously applied to Italy's and Spain's previous NAPs, as well as to the Netherlands' current NAP. However, the plans of Italy and Spain do not meet many of the items on which they have been evaluated. In sections such as monitoring and surveillance of plants, which are clearly lacking, EU countries justified the lack of information with comments such as that European legislation covers most of the items, or that after a prioritisation process, it was decided to not include these. Feedback from the tools' first application was not taken into account. The case of the Netherlands is quite remarkable, because despite having good results in the fight against AMR, they barely include information in their NAP. In addition, the main document is from 2015 and has not been modified since, despite having received feedback from the EU in this regard.[6] A good way to see if enough information is provided in a NAP is by applying an assessment tool, such as the one applied in this study, agreed upon by all twenty-seven EU Member States.

The need of more indicators and targets

Member States and stakeholders consider indicators for human and animal health as the key to secure concrete outcomes.[30] Setting targets facilitates the use of more quantitative tools and thus, helps to obtain more objective evaluation results. However, no targets or objectives were developed for any of the AMR indicators, which makes it difficult to assess progress. The lack of such targets and objectives, in combination with the disparate structures of the NAPs, makes it is difficult to properly compare the countries.

Establishing a set of key structure/process/outcome indicators (e.g., quality indicators, proxy indicators, quantity metrics, on antibiotic use and resistance, AMS and IPC) and targets should be a priority. In addition, such indicators and targets would help to strengthen NAPs. The policy brief developed by the EU – JAMRAI (Join Action Antimicrobial Resistance and Healthcare-acquired Infections) proposed some indicators and targets that are described in Table 2.

Table 2. Proposed AMR indicators and targets examples.[30]

Indicator	Target
Number of antibiotic prescriptions for 1000 inhabitants per year in primary care	< 250
Proportion of children treated with third-generation cephalosporins over the year, out of children receiving antibiotics in primary care	< 3%

The need for an effective One Health approach

The fight against AMR cannot be understood without the perspective of One Health, as it is a multisectoral problem.[31] As can be seen in the assessment, human and animal health take precedence over environmental actions, which has also been observed in earlier evaluations of NAPs.[32] This underscores the importance of environmental monitoring programmes. Furthermore, it is worth noting that existing programmes predominantly centre on water monitoring. However, it has become evident that agricultural land can also harbour a substantial burden of AMR genes. Countries should therefore adopt a holistic approach to comprehensively address AMR.

A better situational analysis

It is essential to develop a proper situational analysis in order to have a good action plan. This point is closely related to the need for more details. In the studied NAPs, many of the actions lack an adequate justification that help to understand the importance or focus given in the NAP. This justification is not hard to make: with millions of cases of AMR yearly across the EU, reducing the disease burden of AMR is important to most countries. It has been estimated that over half a million deaths per year in the EU are due to AMR.[33] Most of the data that countries use in their analysis is based on the data that they have to collect for the ECDC, such as data on antibiotic consumption, resistance of some microorganisms, or antibiotic sales. Countries should gather data that reflects their unique realities, emphasising their individual strengths and weaknesses. Instead of solely relying on obligatory data collection, they should prioritise analysing context-specific information to

gain a more comprehensive understanding of their situation. Italy's plan is good in this regard, as it provides a broad explanation for each block of intervention.

6.2.2. Inter-sectoral coordination mechanism

The need for a clear intersectoral structure

Having a multisectoral approach to tackle AMR that is not only focused on health-related drivers is essential. Firstly, it is well known that diseases are the results of multifactorial causation. Secondly, the health sector requires the services and products of other sectors in implementing various health programmes. Thirdly, development in other sectors can contribute towards the prevention of disease and the promotion of health.[25,34] A previous report by HAI delves deeper into the drivers of AMR that ought to be tackled through a One Health approach.

One Health is a collaborative, multisectoral, and transdisciplinary approach. Thus, NAPs should take into account the collaboration between relevant sectors (government, non-governmental organisations, private sector, etc.).[35] By engaging multiple sectors, partners can leverage knowledge, expertise, reach, and resources, benefiting from their combined and varied strengths as they work toward the shared goal of producing better health outcomes.[36]

In general, all countries could improve in the organisation of these mechanisms, especially the Netherlands, where the structure is not clearly delineated. It is also important to explain how these structures will function. The NAPs should describe the responsibilities of a coordinating mechanism, its membership, and its formal mandate to ensure implementation of AMR policy.

The need to clearly define responsibilities

Spain's NAP provides almost no information about who will oversee the implementation of many of the plans formulated within the NAP, nor is it very clear within the intersectoral structure who will have the responsibility to do so. As a country with a decentralised healthcare system, a clear division of responsibilities is essential. The other two countries' NAPs do provide this information. However, often a long list of government agencies is included, while no information is given about who is responsible for what, or how they are collaborating on implementation. Each countries' NAP can be improved in this regard, making implementation more transparent and accountable, and facilitating learning between countries.

6.2.3. Awareness and understanding of AMR

The need to raise awareness on more than just the consumption of antibiotics in humans

All countries have awareness campaigns, but they focus mainly on human health, targeting the general public and health workers. Previous research on NAPs found that public engagement was generally lacking.[32] Animal health is addressed, but the campaigns and actions in this sector are much less substantial. Food safety and the environment are hardly mentioned in the NAPs.

The need for training in all sectors

The same issue was found for training and professional education: much of the focus is on human and animal health, while the food safety and environment sectors should also be included in AMR training. In Italy, food safety and environmental AMR training is provided only to undergraduates, even though continued professional education is also needed. However, it is the only country that mentions education in all sectors (human health, veterinary, farming, food safety and environment).

6.2.4. Monitoring and surveillance

Monitoring and surveillance plans are generally good if we disregard plants and plant-based food. As mentioned before, countries do not plan for it because it is largely covered by European legislation, and it is not seen as a priority. Nonetheless, incorporating these topics is recommended.

The need for real-time surveillance data

The next step that countries should take in surveillance is moving to a real-time surveillance system. Real-time or near-real-time surveillance systems, in addition to the existing surveillance systems, are key to fight AMR. Real-time surveillance would alert healthcare practitioners in the early phases of an outbreak. This would enable them to promptly institute control measures and case finding, and to ensure adequate access to treatment, thereby reducing morbidity and mortality. With international concerns about emerging infectious diseases, bioterrorism, and pandemics, the need for a real-time surveillance system is at an all-time high. The data generated would also be useful for public healthcare practice, clinical decision making, and research.[37–40]

The need for an environmental surveillance network

Monitoring AMR in wastewater has been proposed as a potential tool to understand the actual prevalence of AMR in the community by monitoring AMR trends and functioning as an early warning system to prevent future outbreaks. It may be done in conjunction with wastewater monitoring for other infectants to limit the implementation burden. In the analysed NAPs, many of the proposals are based on monitoring wastewater, but few systems are implemented, especially in Spain and the Netherlands.

European AMR Surveillance Network in Veterinary Medicine (EARS-Vet)

Countries should consider establishing the European Antimicrobial Resistance Surveillance network (EARS-Vet) as a potential resource for future AMR surveillance in diseased animals. This initiative parallels the success of EARS-Net, as indicated by previous studies.[41] This network could have the potential to fill important AMR monitoring gaps in the animal sector in Europe. Some experts already reached consensus on the combinations of animal species/bacterial species/specimens/production types/antimicrobials to be monitored in EARS-Vet and stress the importance of adding companion animals to be monitored instead of just focusing on food-producing animals.[42]

Most of the countries include plans for monitoring infections in animals. However, the data is not collected using the same variables or units, so it is sometimes difficult to make comparisons. In addition, the surveys that are carried out at the European level are conducted every 10 years, which is too low a frequency in this rapidly changing field. Changes in measurements of 59% were observed in the 10 years between data collection, meaning old data is (nearly) meaningless for current policy.

However, while Spain and the Netherlands have national monitoring systems for AMR in bacterial pathogens in animals, many Southern and Eastern European countries, including Italy, do not. This highlights a major gap in AMR monitoring in Europe, which may make it difficult to implement a European surveillance network.[43]

Expansion of the Healthcare-Associated Infection Network (HAI-Net)
The Healthcare-Associated Infection Network (HAI-Net) coordinates AMR surveillance and antimicrobial use in intensive care and long-term care facilities, and the surveillance of surgical site infections. However, healthcare-acquired infection surveillance in acute hospitals is monitored only once every ten years, so data is scarce and outdated.

6.2.5. Strengthen infection and prevention and control measures

Effective IPC measures are necessary to control the spread of infections, as well as minimise everyday healthcare-acquired infections. Fewer infections in hospitals will result in lower consumption of antibiotics, thereby reducing antibiotic resistance. Both Spain and the Netherlands could improve this by ensuring they plan on IPC programmes at the national level, they have national IPC guidelines, and that this information is reflected in their NAPs.

Fewer infections in animal farms or pets should also result in lower consumption of antibiotics, but all of the NAPs focus almost exclusively on human health, leaving animal health aside. Thus, the three countries must plan and clarify the measures they plan to adopt on this in their plans.

6.2.6. Prudent use of antimicrobials

None of the three countries have planned for restricting the use of specific antibiotics that are crucial for human health. Moreover, Spain and Italy could greatly improve the prudent use of antibiotics in animal health by proposing specific measures restricting and discouraging the use of antimicrobials crucial to human medicine.

Some studies indicated that only three out of ten studied EU countries specifically mentioned that systematic reviews of evidence formed the basis for guideline updates for antibiotic prescription guidelines. In addition, the same research discovered that human and veterinary prescribing guidelines are infrequently updated, making it difficult to include new antibiotics.[44] Further, EU Member States do not reach the same level of achievements concerning health policies on AMS and IPC. In fact, the same study found weaknesses in countries like Spain and the Netherlands due to the absence of national IPC guidelines in their NAPs. All this represents a barrier to the effective implementation of AMS and IPC programmes at the European level, so it is key to develop core elements on AMS and IPC.

6.2.7. Investment/research programmes in the area of AMR

Since 1987, no new class of antibiotics has been discovered, and drug development has largely relied on structural changes to existing compounds. Next to that, due to the efforts to limit antibiotic use because of AMR, especially newer antibiotics, usage is limited, and it is not an attractive market for the pharmaceutical industry. Hence, publicly initiated investment and research programmes in AMR are key in this fight. All countries include plans and strategies for investment and research in this area, though Spain should provide more details about what it is going to investigate.

Nevertheless, the strategies seem to focus on innovation, while there are also many research areas which need more investment, such as the relationship between AMR in the environment and its impact on human and animal health.

6.2.8. Availability of new and old antimicrobial agents

Access to life-saving antibiotics is a global challenge. Some EU countries indicated that shortages of existing antibiotics are a serious problem. They also indicated that this resulted in greater use of broad-spectrum antibiotics, thereby potentially increasing antibiotic resistance. As important antibiotics continue to be unavailable, doctors change prescription habits, potentially away from evidence-informed prescription guidelines. National medicines agencies and procurement agencies lack the tools to work proactively to avoid antibiotic shortages. They know which factories produce the raw materials and finished medicines for their own marketed medicines, but do not have access to data about the global market for a specific medicine. Transparency is needed to better understand supply chain resilience.[45] Further, unpredictable access is not only a challenge for older antibiotics but also for new ones. New antibiotics are not widely available. It is thus imperative that more work be done to ensure the availability of these antibiotics.

7. LIMITATIONS

Written NAPs are not the same as the implementation or execution of all AMR-related policies in a country. In addition, they do not include all the countries' efforts on AMR, so they are not a full reflection of all efforts undertaken. Therefore, the data on the quality of NAPs should not be extrapolated to draw conclusions on whether the full approach of the various countries is effective. However, a well-written and extensive NAP, when implemented, facilitates the fight against AMR, so it is a useful measure of policy in the studied countries.

Only secondary data was used for the various data visualisations in this study. Regarding the data used in this study, to facilitate reliability, the coding of the various variables is extensively explained in Chapter 5. The coding of the data was done by various researchers to increase the reliability.

8. CONCLUSION

The rates of antimicrobial usage show substantial disparities among Italy, Spain, and the Netherlands, with certain regions struggling with alarmingly high levels of consumption. As this study underscores, the intricate relationship between antimicrobial use and the emergence of resistance remains a pressing concern. The data collected in this study corroborates this connection. Moreover, it is worth emphasising that the southern countries within our analysis have witnessed a disproportionately significant surge in resistance. This emphasises the pressing need to intensify the fight against AMR in these regions.

It is essential to develop, improve and implement NAPs on AMR from a One Heath perspective. It becomes increasingly imperative for healthcare systems, policymakers, and stakeholders to collaborate on multifaceted strategies aimed at curbing excessive antimicrobial use while fostering prudent prescribing practices. A holistic approach, encompassing not only rigorous surveillance but also public awareness campaigns,

infection prevention measures and AMS programmes, is essential to mitigate the burgeoning threat of AMR and safeguard the effectiveness of these vital medications for future generations. Moreover, it is crucial not to neglect animal health and the environment, as has unfortunately been the case in the evaluated NAPs. Countries could further improve their efforts by working with a similar structure to develop their NAPs, expanding their monitoring and surveillance to the environment, and restricting certain antimicrobials for human and animal use to preserve their efficacy against antimicrobials.

Finally, it is crucial to acknowledge the commendable progress and extend our congratulations to Italy for its comprehensive and robust plan addressing AMR. We recommend that the Netherlands contemplate revising and updating its NAP, while encouraging Spain to persist in its diligent efforts and concentrate on the key areas emphasised in this study, such as research initiatives and targeted measures in animal health.

If no effective public health action is undertaken in the coming years, AMR and its impact will undoubtedly grow further.

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