

National Antibiotic Resistance Policy and Implementation in Spain: Challenges, Opportunities, and Recommendations

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Executive Summary

The ability of microbes to develop and disseminate mechanisms of antimicrobial resistance (AMR) poses a serious risk to the long-term sustainability of antimicrobial treatments, affecting patients seeking safe life-saving treatments for infections and cancer as well as surgery and other treatments. This imminent threat encroaching on our hospitals, primary health centres, and communities has led to scientific and global government organizations to mobilise actors in the fight against AMR. As a response recommended by the European Commission, many European states have implemented national action plans (NAP) to combat AMR, including Spain, introducing in 2014 the *Strategic Action Plan to Reduce the Risk of Selection and Dissemination of Antibiotic Resistance* (PRAN) 2014-2018.

In this study, Spain's NAP was mapped according to the European Commission and European Council action plan and recommendations. Frameworks and action plans published following the WHO's 2015 Global Action Plan were also used to analyse the implementation plan of the PRAN. Strengths included actions to improve surveillance and implement local antimicrobial stewardship programs while weaknesses comprised of a lack of actions to improve collaboration amongst stakeholders and a well-organized implementation and monitoring and evaluation plan.

A questionnaire was designed and administered to Spanish experts in AMR on barriers, actions to improve scope and implementation of the PRAN, and recommendations. The questionnaire found there was no hierarchy in relevance of barriers. One possible explanation for this is the One Health framework the PRAN is based in emphasizes intersectoral collaboration. Recommendations based on findings were compiled, with chief potential barriers to their implementation – as mentioned by experts – being political commitment and coordination. Findings from this study may be used to evaluate the evolution of the PRAN with the introduction of the new NAP in 2019, to ensure Spain is building on strengths and addressing weaknesses.

Abbreviations

AC: Autonomous Community
 AEMPS: Spanish Agency of Medicines and Medical Devices
 DALY: Disability-Adjusted Life Year
 EEA: European Economic Area
 ESVAC: European Surveillance of Veterinary Antimicrobial Consumption
 MSSSI: Spanish Ministry of Health, Social Services, and Equality
 AMR: Antimicrobial Resistance
 AMS: Antimicrobial Stewardship
 ECDC: European Centre for Disease Prevention and Control
 EPHA: European Public Health Alliance
 EU: European Union
 FAO: UN Food and Agriculture Organization
 NAP: National Action Plan
 MS: Member State
 OIE: World Organization for Animal Health
 PRAN: *Strategic Action Plan to Reduce the Risk of Selection and Dissemination of Antibiotic Resistance*
 REIPI: Spanish Network for Research in Infectious Diseases
 R&D: Research and Development
 WHO: World Health Organization

1. Introduction

1.1 Background

The introduction of antibiotics in the early 20th century was a major turning point in modern medicine [1]. Due to their high efficacy and ability to significantly decrease morbidity and mortality from bacterial infections we have seen an increase in life expectancy like never before [2]. However, with the discovery and subsequent use of antimicrobial agents, we have also seen a rapid rise of antimicrobial resistance (AMR)[3]. Although AMR is a naturally occurring phenomenon that is a by-product of pathogen evolution, the misuse and abuse of antimicrobial agents by healthcare providers, patients, veterinarians, and agriculturalists has led AMR to grow and spread at uncontrollable rates [1]. The unique nature of microbes to share genes vertically, in conjunction with their ability to exchange genes horizontally has enabled AMR genes to be efficiently selected for and rapidly disseminated throughout microbial populations [3]. Different mechanisms of sharing AMR gene mutations in microbial populations combined with selective pressures from improper use of antimicrobials has led to a rapid and wide spread of resistance globally, paradoxically creating new untreatable diseases leading to morbidity and mortality [1-4].

Antibiotic resistance discovery pre-dates the discovery of penicillin, when scientists observed a bacterial resistance to the synthetic drug “Salvarsan”, used to treat Syphilis [5]. The issue of antibiotic resistance was publicly announced as early as 1945, in Alexander Fleming’s Noble lecture, in which he warned of the dangers of underdosage and misuse of antibiotics. The discovery of horizontal transmission of AMR through mobile genetic elements (later to be known as plasmids) in the 1960s made the prospect of widespread AMR a more pressing concern [6]. In 1981, clinician-scientist Stuart Levy convened an international conference in the Dominican Republic on the “Molecular Biology, Pathogenicity and Ecology of bacterial infections” in which an official joint statement signed by scientists from 27 different countries pointed to antibiotic resistance as a “worldwide public health problem”[6]. Although the World Health Organization (WHO) began establishing working groups and organized meetings to discuss AMR as early as the 1970s, they did not formally recognize the rise of AMR as a global threat until 1998, with a call for a united global front to fight AMR [7]. According to the European Centre for Disease Prevention and Control (ECDC), 25000 patients died annually between 2011-2015 due to antibiotic resistant bacterial infections in the European Union (EU) alone [8-10].

AMR is a global health issue, affecting high income, low income and middle-income countries around the world. Reports, guidelines, and other publications by international organizations such as the UN Food and Agriculture Organization (FAO), World Organization for Animal Health (OIE) and the WHO, signified increased awareness leading to international collaboration. These collaborations which were born out of international summits, such as the Trans-Atlantic Taskforce on Antimicrobial Resistance in 2009, focused on prudent use of antimicrobials in animals and humans, infection prevention, and development of new antimicrobials[11]. The EU council, European Parliament, and European commission and its agencies began publishing resolutions leading to a European Action Plan to combat AMR in 2011[12]. This Action Plan outlined 12 actions to be developed and implemented within the

Member States (MS) within 5 years. In March 2012 the Ministry of Health, Social Services, and Equality (MSSSI), began gathering a multidisciplinary working group to help develop, create, and implement an intersectoral action plan at a national scale. In July 2012, the Spanish Agency of Medicines and Medical Devices (AEMPS) called the first meeting of the working group, and began coordinating and developing a national strategic action plan [13]. Spain introduced the “*Strategic action plan to reduce the risk of selection and dissemination of antibiotic resistance*” in 2014 in accordance with guidelines set by the European Commission, conclusions of the European Council, and WHO European Region recommendations.

To assist MS to implement EU Council recommendations on the prudent use of antimicrobial agents (2002) and EU Council conclusions on AMR (2008), the ECDC developed a process of country visits to assess and discuss prevention and control of AMR in host countries. In 2016, at the invitation of the MSSSI, an ECDC delegation team conducted meetings and discussions to provide an evidence-based assessment on the prevention and control of AMR efforts in Spain to provide conclusions and recommendations [14].

A high incidence of AMR isolates and antibiotic resistant infections in Spain compared to the EU average [9] indicates an ever-present national problem for preventing bacterial infections and control of the spread of AMR. Cassini et al. calculated Spain to have the second highest burden in DALYs from penicillin-resistant *Streptococcus pneumoniae* [15]. Furthermore, a 2017 surveillance report by the ECDC reported Spain to be the largest European consumer of antibiotics in the primary care setting [16]. Although, Spain ranked much better among EU/EEA member states in antibiotic consumption for systemic use in the hospital sector, it did not report surveillance data until 2017, still falling above the EU/EEA member states average in 2017 [16]. The 2016 Special Eurobarometer on antimicrobial resistance reported 42% of Spanish respondents claimed to have used antibiotics in the last year, the third highest rate among 28 EU countries polled, and a 4% national increase from 2013 [17]. According to data collected by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), Spain is the largest consumer of veterinary antimicrobials of the 30 European countries that provided data [18], with an increase in sales by 1000 tonnes from 2010 [19] and making up 1/3 of the overall purchases of antimicrobials of participating countries, by weight [18]. Additionally, Spain on average consumed more than double the average amount of antimicrobials per kg of bodyweight of food-producing animals than any of the other 30 European countries [18].

The purpose of this study is to utilize the frameworks, strategic plans, and guidelines published by the WHO and European Commission as well as other national action plans of European MS as a focal point for analyzing the current state of the antibiotic resistance efforts in Spain. The analysis will look to identify strengths and weaknesses in national Spanish policies and implementation of these policies. By comparing Spain’s NAP and government initiatives in AMR stewardship to national policies in countries showing improved trends in antibiotic consumption and control of antibiotic resistance, key barriers in Spain’s approach to control antibiotic resistance and policy implementation were identified. Spanish policy was evaluated based on recent guidelines provided by international governing bodies (EU and WHO) and recommendations made by international agencies. Furthermore, Spain’s implementation

plan was appraised, based on guidelines published by the WHO and other international governing bodies, to identify possible barriers to effective control of AMR. Using the NAP as an outline of Spain's approach and as a collection of indicators of the status and breadth in the effort to mitigate AMR, recommendations on improving the Spanish plan and its implementation were presented to Spanish AMR experts in the field. Using this as a platform to combine the opinions of the broad spectrum of stakeholders from different regions of Spain, the recommendations proposed by the ECDC's *Country Visit to Spain to Discuss Antimicrobial Resistance Issues*[14] was also presented to experts for feedback.

Effective NAP across Europe, designed and implemented based on international guidelines set by the EU and WHO have shown great success in controlling AMR and diminishing antimicrobial consumption [20]. Therefore, this study looks to identify strengths of effectively implemented NAP, weaknesses of the Spanish NAP, and barriers and roadblocks in implementation. This information will be used to create recommendations to propose to professionals in the field to improve the implementation of the Spanish NAP, reduce antimicrobial consumption, and decrease the burden of bacterial infections.

1.2 Hypothesis and Objectives

We hypothesized a well organized, intersectoral, and thorough NAP coordinated and developed by the AEMPS in collaboration with multiple interdisciplinary actors will follow recommended actions listed by European Commission's action plan of 2011 and EU council conclusions of 2012[12, 21]. However, actions adapted for a Spanish context will show differences from the original actions proposed by international bodies. Deviations from recommendations made by international bodies will be a factor in the hindered control of AMR on a national level in Spain. Furthermore, we believe implementation of policies will become a more urgent issue in AMR control and will show to be a crucial target for intervention and recommendations most likely to yield both short- and long-term impact.

Objectives of the study include:

- Mapping Spanish policies using guidelines set by European and Global Organizations in AMR policy and stewardship to identify strengths and barriers to implementation of AMR policy in Spain
- Propose recommendations for improving policies and strategies for implementation of existing and recommended policies in Spain to decrease antimicrobial consumption and control spread of AMR
- Organize recommendations by relevance and feasibility in Spain based on expert opinions

2. Methodology

Spain's PRAN developed by the AEMPS was analyzed using preceding guidelines, recommendations, and conclusions put forward by the EU council, the European Commission and its agencies, and the WHO on the prudent use of antibiotics and infection control and AMR. Actions and objectives in the PRAN were compared to actions and objectives in existing guidelines, recommendations, and action plans published by international organizations (EU and WHO) to establish the thoroughness and comprehensiveness of the Spanish national plan. Furthermore, recommendations and strengths of the PRAN from the analysis of EU/EEA MS by the European Public Health Alliance (EPHA) 2018 study [22] to analyze the status of

NAP development in Europe, were also compiled and summarized. A questionnaire was designed using findings, which included recommendations made based on strengths and weaknesses identified in the PRAN, and proposed to stakeholders in Spain.

2.1 Policy Mapping:

The PRAN was mapped using the European Commission's Communication of November 17, 2011, establishing an *Action plan against the rising threats from Antimicrobial Resistance* [12] to evaluate strengths and weaknesses in Spain's NAP compared to the EU approach. The 6 strategic lines of the PRAN and 5 aims of the European Commission's action plan were combined into 6 different categories: 1) infection prevention, 2) antimicrobial stewardship, 3) surveillance of infections, AMR spread, and antibiotic consumption, 4) R&D in diagnostic tools, treatments, transmission, and prevention (i.e. vaccines), 5) intersectoral collaboration at all levels of governance, and 6) knowledge, awareness, and professional training. 76 actions from the PRAN and 38 interventions mentioned in Section 2 and 3 of the European Commission action plan were then classified into these 6 categories. Proportional distribution of actions in each plan were mapped using a radar chart.

The PRAN also cited the 12 aspects listed in point 29 of the EU Council Communication of June 22, 2012 *Council conclusions on the impact of antimicrobial resistance in the human health sector and in the veterinary sector – a "One Health" perspective*[21] as a basis for pursuing a One Health approach. The PRAN was mapped using the EU Council's communication of June 2012 as a framework for measuring adherence to the recommendations made as well as to the One Health approach. A checklist was made of the 12 aspects listed by the EU council. PRAN's measures covering aspects and incorporation of human health sector and veterinarian sector into actions addressing these aspects (where applicable) were mapped.

Additional action plans, guidelines and recommendations made by international organizations such as the WHO, EU council and EPHA published in the years after the publication of Spain's NAP were also compared to the PRAN, including:

- WHO Global Action Plan on Antimicrobial Resistance (2015) [23]
- WHO, FAO, & OIE's Antimicrobial Resistance: A manual for developing national action plans (2016) [24]
- European Council's EU Guidelines for the prudent use of antimicrobials in human health (2017)[25]
- EPHA's Translating Political Commitments into action: The development and implementation of National Action Plans on Antimicrobial Resistance in Europe (2018) [22]

A review of these guidelines and action plans was conducted to extract potential strategies, actions, and additional components to improve the scope and implementation plan of the PRAN.

2.2 Questionnaire

Design:

Information on the barriers in controlling AMR and implementation of a NAP on AMR from policy mapping was compiled in a list of relevant barriers in Spain. Additional proposed and/or implemented actions in other settings (global, national or regional) were collected and summarized as potential strategies and targets to expand the scope of the PRAN and improve its implementation. Strengths, weaknesses, and barriers from findings in the policy mapping were used to provide recommendations to improving the Spanish NAP's implementation plan.

All the information from the policy mapping was compiled into an online questionnaire. This online questionnaire was administered to stakeholders to verify the findings from mapping Spain's NAP. The online questionnaire inquired on barriers in the Spanish context, actions to expand the scope and implementation of the NAP, and further recommendations.

Scheme:

The questionnaire was a mixed methodology. Experts were asked to score barriers and actions to improve the scope of the existing action plan as well as its implementation, based on relevance, priority, feasibility, and immediate and long-term impact. Recommendations from findings in the review of the literature were also scored based on relevance in the present Spanish context. Additionally, recommendations from the ECDC country visit to discuss AMR in 2016[14] were also provided to experts for scoring.

The questionnaire also included open-ended questions to gain further input from experts on barriers, existing programs for implementation, and feasibility of implementation of NAPs and recommendations. Responses were combined based on common programs listed, and barriers in feasibility and implementation mentioned.

The questionnaire was divided into 3 main sections:

1. **Barriers:** 10 potential challenges in battling AMR in Spain were posed to experts to gain insight into what are the main barriers to controlling AMR and how severely these challenges hinder effective implementation of the PRAN. Experts were also asked to provide any other potential challenges they have experienced or been exposed to in their careers working on AMR and existing or potential interventions to mitigate these barriers.
2. **Scope and implementation:** 10 strategies, actions, and recommendations from action plans, conclusions, and reports published by international organizations (primarily WHO and EU) were compiled from the policy mapping and posed to experts. Experts were asked to evaluate these actions based on: priority of introduction of actions, feasibility of implementation, immediate impact, and long-term impact. They were also asked to provide any other existing public interventions in their field and/or region for combatting AMR.
3. **Recommendations:** 9 recommendations to improving implementation of the PRAN as well as 14 recommendations proposed by the ECDC[14] were scored by experts based on relevance. Furthermore, experts were asked to elaborate on the potential feasibility and challenges of implementing these recommendations.

Participants:

Stakeholders from government organizations, ministries, professional associations, scientific societies, collegiate associations, and committees were contacted to complete the questionnaire. Questionnaires were administered to a selection of clinicians, veterinarians, academics, and policymakers directly involved in control and regulation, sale, consumption, and surveillance of antimicrobials and implementation of programs for the control of antimicrobial use. Participants were selected with the intent of achieving representation from different sectors of antimicrobial consumption and control addressed in the NAP such as: health, agriculture, and veterinary sectors, as well as hospital workers, administrators and academics.

Participants contacted represented a wide array of institutions and fields of practice and research. Sources contacted for questionnaire completion included:

- Spanish Network for Research in Infectious Diseases (REIPI)
- List of Participating Experts in working groups of PRAN 2014-2018
- Foodborne Zoonoses and Antimicrobial Resistance Unit, Centre for Veterinary Health Surveillance, Universidad Complutense Madrid
- Primary Health Care and Community Services, Institut Català de la Salut
- Spread of questionnaire by respondents to secondary contacts (Snowball effect)

Analysis:

Demographic information on the respondents was collected and respondents were classified based on geography and field of expertise. Means of responses and standard deviations (SD) were calculated. Means of responses were ranked to identify any trends in expert opinions and SD was used to evaluate consensus. Mean and SD for each respondent were also calculated to measure the variability within an individual's own responses. Responses from open-ended questions were translated from Spanish to English using DeepL.com and verified by a native Spanish speaker. Responses were grouped based on common themes. Responses were kept anonymous.

Respondents were grouped into major fields of expertise and data was analysed based on scoring of relevance of barriers and priority, feasibility, immediate impact, and long-term impact of further actions to improve scope of the PRAN. Means of responses and SD were calculated. Range and standard error of the mean were calculated for the means of responses within each profession to evaluate the distinguishability between categories in each section.

3. Results

3.1 Policy mapping:

3.1.1 European Commission Action Plan and EU council Communication

The Spanish PRAN was mapped according to the EU Commission's 2011 Action plan to identify strengths and weaknesses in the PRAN compared to the EU approach. Specific actions from each plan were categorized into 6 focus areas: 1) infection prevention 2) antimicrobial stewardship 3) surveillance of infections, AMR spread, and antibiotic consumption 4) R&D in diagnostic tools, treatments, transmission, and prevention (i.e. vaccines) 5) intersectoral collaboration at all levels of governance, and 6) knowledge, awareness, and professional training. The proportion of actions addressing each area of focus was calculated and the action plans were plotted on a radar chart (fig.1). In comparing the action plans, it is evident that a lower proportion of actions in the PRAN were dedicated to multilateral and

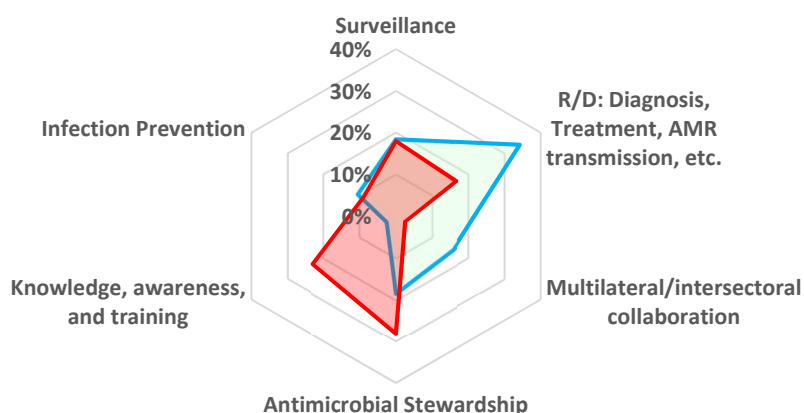


Figure 1. Radar chart comparing scope and adherence of PRAN 2014-2018 (Red) to European commission's 2011 Action plan against the rising threats from Antimicrobial Resistance (Blue). Proportions were measured as percent of actions in each category.

intersectoral collaboration and R&D in improved diagnostics, treatments and treatment criteria/guidelines, and understanding AMR transmission and mechanisms, in comparison to the EU commission action plan. A higher proportion of actions in the PRAN were dedicated to knowledge and training of stakeholders and professional education and antimicrobial stewardship compared to the EU commission action plan. A similar proportion of actions in the PRAN and the EU Commission action plan were focused on infection prevention and surveillance.

The PRAN was also mapped using the EU Council's communication of June 2012 as a framework for measuring adherence to the One Health approach. The 12 elements for inclusion listed by the EU council's call for MS to implement NAPs (June 2012 EU council conclusion, point 29) [21] were used as a framework for categorizing the 20 measures of the PRAN. Measures were organized into categories and adherence to the One Health approach was evaluated based on inclusion of human health and animal sectors in actions that made up the respective measures. Specific measures addressing each category were also included (Table 1). Of the 12 elements, 10 were addressed in the PRAN with adherence to the EU council's One Health approach. 4 elements were specific to either Human Health sector or Animal Health sector. 2 Elements listed in the EU council's conclusions were not included in measures of the Spanish NAP.

Table 1. Mapping PRAN 2014-2018 according to point EU council's conclusions on the impact of antimicrobial resistance in the human health sector and in the veterinary sector – a "One Health" perspective (2012), point 29. Green checkmark: Addressed in at least one measure of PRAN 2014-2018. Red X: not addressed in any measure of PRAN 2014-2018. N/A: Category does not involve sector in implementation.

Categories	Animal Health	Human Health	Specific Measures present in PRAN
Prudent use guidelines	✓	✓	II.1-II.3, III.1, III.3, IV.2, V.1, V.4, I.1
Ensuring diagnostic/susceptibility based treatments	✓	✓	II.1-2, III.2, IV.1
Education and training	✓	✓	III.1, III.4, V.1-3,
Prevention of illegal use	✗	✗	
Limit use of critically important antimicrobials	✓	✓	I.3
Limit prophylactic use	✓	✓	II.4
Limit use in animal herds	✗	N/A	
Improve animal health and infection prevention	✓	N/A	III.1, IV.1
Comparable and intersectoral surveillance	✓	✓	I.2, II.1, I.1, IV.2
Sales consumption surveillance in humans	N/A	✓	I.1, IV.2
Sales consumption surveillance in animals	✓	N/A	I.1, IV.2
Monitor intersectoral implementation	✓	✓	I.4, II.1

3.1.2 WHO, EU and EPHA publications post-2014

The WHO published a Global Action Plan on AMR in 2015 [23]. The action plan was published to provide a framework for NAP to combat AMR. Under paragraph 2, the Global Action Plan states: "It is expected that countries will develop their own national action plans on antimicrobial resistance in line with the global plan". Encompassing 5 objectives, the main goal of the action plan is to ensure longevity of effective treatment, implementation of sustainable infection prevention and equality of access to safe and quality-assured medicine. It goes on to outline the major stakeholders in battling AMR. The 6 strategic lines of the PRAN align well with the WHO Global Action Plan. However, one key difference is the focus in the global action plan on capacity for developing interventions, resources available, and sustainable streams of funding and resources for developing and implementing actions, strategies, and interventions.

Additionally, The Global Action Plan lists 5 principles that all action plans should follow:

1. whole-of-society engagement, including "One Health" approach
2. prevention first
3. ensuring access while avoiding excess
4. sustainability of interventions
5. incremental targets for implementation

The PRAN aligns well with principles 1. and 2. However, there are no actions addressing the issue of access, sustainability of interventions, and no targets of implementation are mentioned. In 2016, the WHO published *“Antimicrobial Resistance: A manual for developing national action plans”*. The guiding principles mention alignment with the WHO Global Action plan, as well as a step-wise approach and prioritisation of actions and implementation as key to developing an effective NAP. Furthermore, the manual also describes three key components of a NAP: 1) strategic plan, 2) operational plan, and 3) monitoring and evaluation (M&E) plan (Figure 2)[24].



Figure 2. Core components of a NAP: Summary of key concepts. Adapted from: *“Antimicrobial Resistance: A manual for developing national action plans”*[24]

The manual emphasizes the importance of implementing a strategic plan with objectives that are: specific, measurable, achievable, relevant, and time-bound. The most evident omission in the development and incorporation of actions in the PRAN is the absence of any timeline. Furthermore, some of the wording of actions provide an ambiguity in who is responsible for accomplishing these goals, who will be leading the way in their implementation, and who will be most affected by these actions. Details of the operational plan – including the activity work plan and budgeting plan – are also omitted from the PRAN. The M&E plan is not clearly outlined in the PRAN. However, an annual report on progress made, targets, and objectives is mentioned in the PRAN. Nevertheless, intended goals and targets are not mentioned in the PRAN.

The EU guidelines for prudent use of antimicrobials, published in 2017 were mainly focused on improving responsible use of antimicrobials, decreasing excessive use of antimicrobials, and introducing elements of good practices to be exercised by healthcare professionals. These guidelines are presented, listed, and described in relation to each stakeholder involved in AMR control and spread. Although all actions in the Spanish NAP are divided into health sector, animal sector, or both sectors, further information as to which stakeholders specifically are to be made responsible for carrying out the actions, their implementation, and their monitoring is not included. Furthermore, other sectors and stakeholders apart from health, animal, and agriculture sectors, such as the financial sector, environmental sector, business sector (i.e. industry) are not well integrated into the PRAN.

In 2018, the EPHA published the study titled “Translating Political Commitments into action: The development and implementation of National Action Plans on Antimicrobial Resistance in Europe”. This study summarized the status of development and implementation of European MS NAPS on AMR based on 4 primary criteria. This framework was applied to all available EU/EEA MS action plans at the time, including the Spanish PRAN. A country profile was included, identifying strengths and weaknesses of the PRAN based on 4 thematic areas: coverage of a One Health approach, identification of funding sources and budget estimates, implementation and integration of evaluation and progress monitoring mechanisms, and inclusion of measurable targets. Key strengths identified in the Spanish plan include a consistent inter-sectoral approach, proposing actions in the human health sector and animal sector and the elaboration of strategic areas into specific measures, further divided into specific actions to implement. A key weakness identified in the analysis framework is the lack of budgeting and measurable targets from the PRAN. The key barrier to implementation of the PRAN in Spain identified the complexity of collaboratively implementing the inter-sectoral approach in Spain’s 17 individually managed and funded Autonomous Community healthcare systems.

3.2 Questionnaire

Online questionnaires were sent by email to experts professional networks as described in the methodology. Questionnaires were made available May 14-June 7, 2019, with reminder emails sent over this period. Thirty-three fully or partially completed questionnaires were submitted. The list of participants and their institutions are shown in Annex Table 1. 73% of participants agreed for their names and institutions to be cited, with 65% stating interest in further participating in this project. 23% of participants requested to remain anonymous.

Based on demographic data collected, respondents represented 10 of the 17 Autonomous Communities (Figure 3), including:

- Madrid (10)
- Catalonia (7)
- Andalusia (6)
- Aragon (3)
- Cantabria (2)
- Castilla y Leon (1)
- La Rioja (1)
- Valencia (1)
- Balearic Islands (1)
- Canary Islands (1)

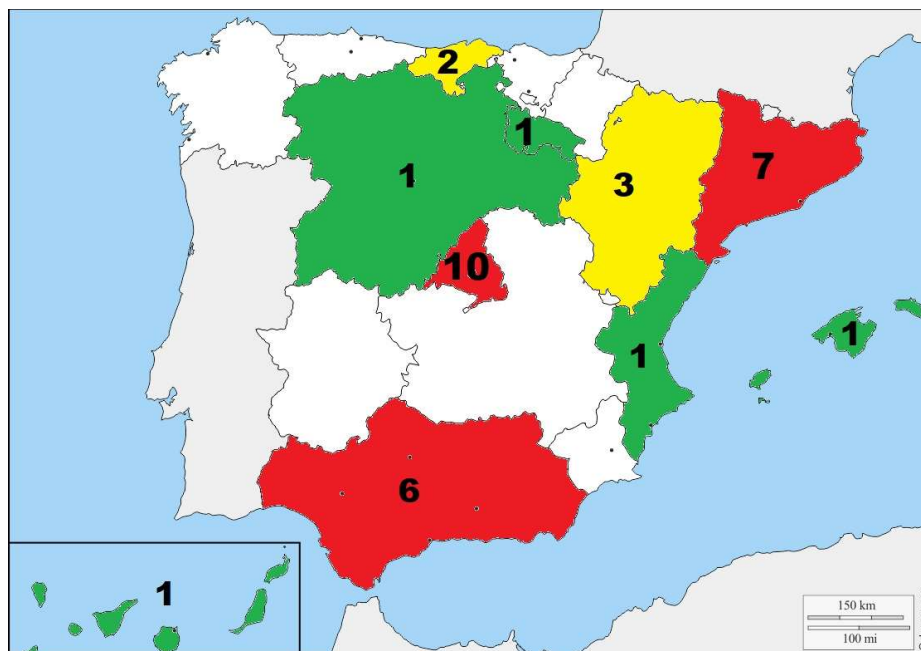


Figure 3. Map of Spain showing geographical distribution of respondents in online questionnaire. Represented as number of participants from each Autonomous Community. Red: >5 representatives; Yellow: 2-5 representatives; Green: individual representative.

Data on field of expertise of respondents was also collected and summarized below. Experts were divided into sectors based on self-reporting in the questionnaire. As Figure 4 shows, a majority of respondents self-identified as either physicians (37%) or Veterinarians (practicing or research) (20%). As all of the respondents were either simultaneously or at some point involved in practice, research, and/or policymaking, experts were not categorized based on role.

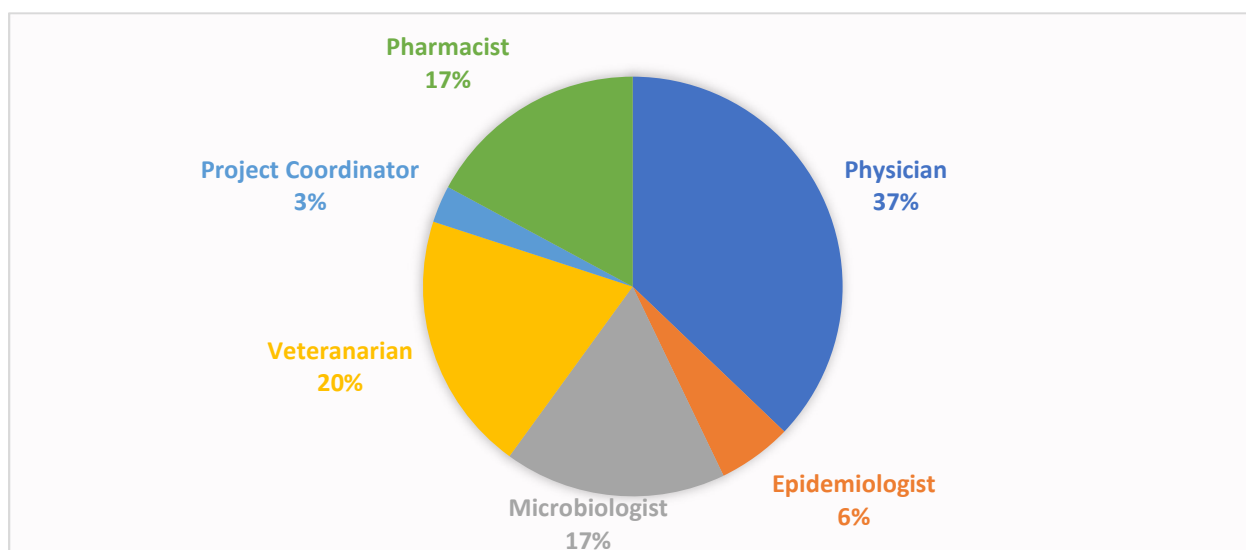


Figure 4. Pie chart representing respondents based on self-reported profession in online questionnaire.

3.2.1 Questionnaire responses on barriers, actions and recommendations

Barriers

Mean relevance score for each person in the barriers categories was 7.22 (Range=3.7-9.7; SD: 1.76) with the mean SD of each respondent at 1.07 (Range=0-3.03, SD=0.69). 9.1% of respondents had an SD of 0, indicating they did not indicate any difference between the barriers. 54% of respondents had an SD below 1.1, indicating very low discriminatory power (only selected 2 or 3 values) (Supplementary Table 2).

Overall, the barrier that received the highest relevance score was “infection prevention and control in community and hospital settings” (7.8). Four barriers scored 7.1 on relevance, including: “One Health approach and collaboration”, “Autonomous Community collaboration and commitment”, “R&D funding”, “Access to high quality medicine and treatment”, and “Political and financial commitment”. The range of relevance was 7.1-7.8. High SD values indicate high variance among responses, ranging from 1.7-2.4 (Figure 5).

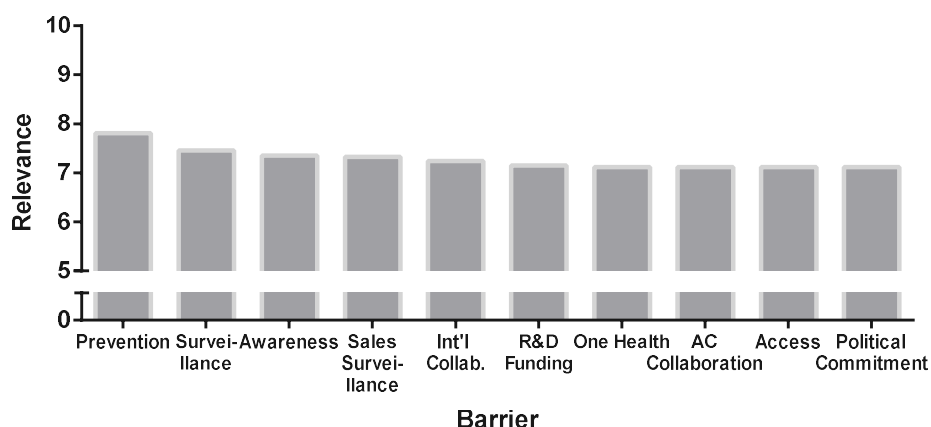


Figure 5. Barriers to fighting AMR in Spanish context. 33 respondents scored barriers on scale of 1-10 based on relevance, with higher score indicating higher relevance. Mean score for each barrier was calculated.

In asking for additional barriers in the Spanish context 33% agreed the above barriers sufficiently covered the barriers faced in controlling AMR. The other responses were divided into 5 groups: 1) lack of public awareness and disinformation 2) Insufficient education and training of professionals in AMR 3) Discoordination and conflicts between stakeholders and interests 4) Lack of regulation of prescription and dispensing 5) Inadequate political and financial/budgetary commitment.

Respondents were asked to describe examples of best practices and local interventions aimed at addressing some of these barriers. 58% of respondents provided examples that focused on 4 main aspects of interventions: 1) Regional level programs, interventions, and guidelines (mainly PROA), 2) R&D in antibiotics, alternative antimicrobial treatments, and prevention/vaccines 3) Guidelines for better diagnosis practices 4) Implementing good practices in veterinarians use.

Expanding scope and implementation of NAP

Mean priority score for each respondent in the actions categories was 8.59 (Range=6.5-10; SD: 0.82) with the mean SD of each respondent 1.11 (Range=0-3.21, SD=0.59). 3% of respondents had an SD of 0, indicating they did not indicate any difference between the actions. 61% of respondents had an SD

below 1.1, indicating very low discriminatory power (only selected 2 or 3 values). The SD in the table represents the variability between respondents (Supplementary Table 3).

In calculating mean priority scores, the range was 7.8-9.2. Only 2 actions averaged a score above 9: “Antimicrobial stewardship and infection control”, and “development and implementation of better diagnostic tools”. These also had the lowest SD (0.89 and 0.81, respectively), indicating a higher level of consensus. The lowest scoring actions listed in terms of priority was “effectiveness and cost-effectiveness research” and “ensuring access to quality essential medicine” (7.8 and 8.1 respectively) (Figure 6A).

Mean feasibility score for each respondent in the actions categories was 7.29 (Range=6-9.8; SD: 0.87) with the mean SD of each respondent 1.22 (Range=0.52-2.01, SD=0.37). 42% of respondents had an SD below 1.1, indicating very low discriminatory power (only selected 2 or 3 values). The SD in the table represents the variability between respondents (Supplementary Table 3).

The range of feasibility scores was 6.4-8.0. “Strengthening surveillance” was the action seen as most feasible for improved implementation with a score of 8.0 (SD=0.97). Better implementation of a “multi-sectoral “One Health” approach” was seen as the least feasible (Figure 6B).

Mean immediate impact score for each respondent in the actions categories was 7.08 (Range=4.7-9.5; SD: 1.35) with the mean SD of each respondent 1.40 (Range=0.70-3.01, SD=0.56). 39% of respondents had an SD below 1.1, indicating very low discriminatory power (only selected 2 or 3 values). The SD in the table represents the variability between respondents (Supplementary Table 3).

The range of immediate impact scores was 6.2-8.0. Better implementation of a “multi-sectoral One Health approach” and “effectiveness research” were believed to be the least impactful in the short term. “Development of better rapid diagnostic tools”, “strengthening surveillance”, and “antimicrobial stewardship and infection prevention” were believed to be most impactful in the short term (Figure 6C).

Mean long-term impact score for each respondent in the actions categories was 8.56 (Range=6.3-10; SD: 0.97) with the mean SD of each respondent 1.06 (Range=0-2.53, SD=0.59). 3% of respondents had an SD of 0, indicating they did not indicate any difference between the actions. 48% of respondents had an SD below 1.1, indicating very low discriminatory power (only selected 2 or 3 values). The SD in the table represents the variability between respondents (Supplementary Table 3).

Scores in Long-term impact ranged from 7.6-9.1. Similar to immediate impact, “development of better rapid diagnostic tools” and “antimicrobial stewardship and infection prevention” were believed to have the highest impact in the long term, along with “increasing awareness and promotion of appropriate use of antimicrobials”, a “regulatory framework for prudent use of antibiotics in animal medicine”, and “strengthening surveillance”. “Effectiveness research” was the lowest scoring intervention in terms of long term, being the only intervention to average as score below 8 (Figure 6D).

In comparing all the categories, Long-term impact and priority (both 8.6) averaged higher scores than feasibility and immediate impact (7.3 and 7.1, respectively) (Figure 6).

Respondents were then asked for any additional actions to improve the scope of the national action plan (while keeping aligned with the “one health” approach) and its implementation. 67% did not suggest any additional actions to improve the scope or implementation of the national action plan.

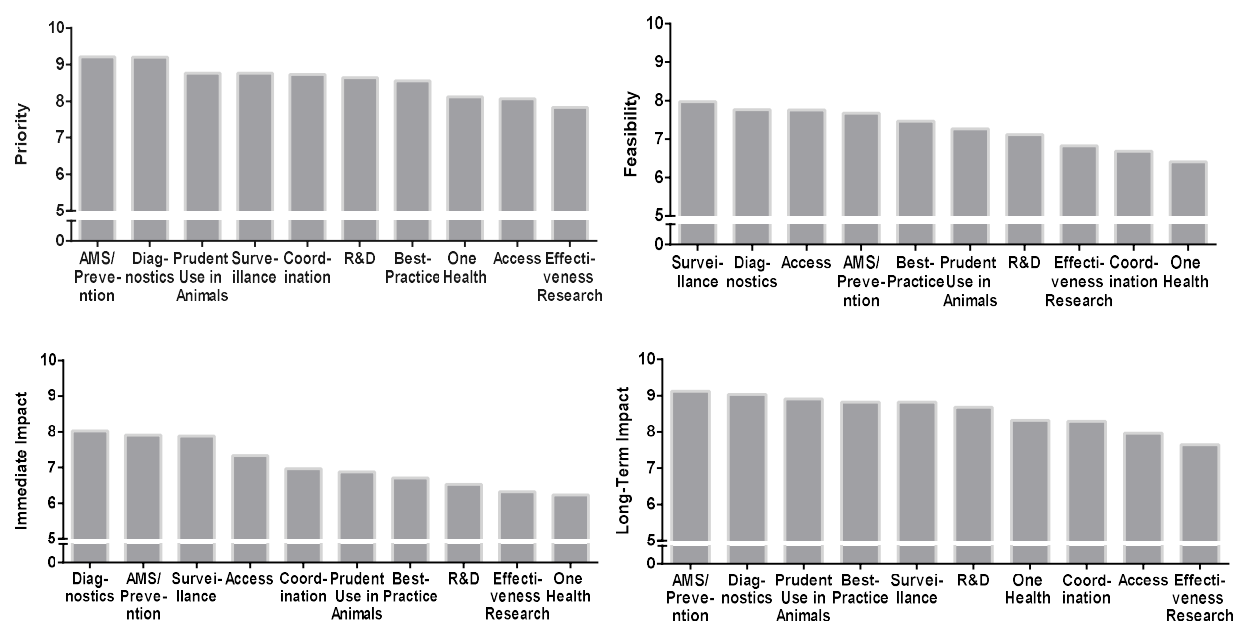


Figure 6. Actions to expand the scope and improve implementation of the PRAN. 33 respondents ranked proposed actions based on 4 criteria: priority of introducing action to improve scope and implementation of PRAN (top left), feasibility of introduction (top right), potential immediate impact (bottom left), and potential long-term impact (bottom right). Each criterion was evaluated on a scale of 1-10, with higher scores indicating better outcome under respective criterion. Results are represented as mean of responses.

Respondents focused on 4 main areas for improving the PRAN in a One Health oriented approach: Expanding one health scope to include more sectors/intersectoral coordination, outreach campaigns and interventions in population, training and education programs, and R&D in alternative antimicrobial treatments and vaccines.

Recommendations for PRAN implementation plan

Mean relevance score for each person in the recommendations for implementation categories was 8.24 (Range=6.44-9.89; SD: 1.10) with the mean SD of each respondent 1.01 (Range=0-3.04, SD=0.65). 6.1% of respondents had an SD of 0, indicating they did not indicate any difference between the recommendations. 70% of respondents had an SD below 1.1, indicating very low discriminatory power (only selected 2 or 3 values). The SD in the table represents the variability between respondents (Supplementary Table 4).

The experts gave a small range of relevance scores between the recommendations for improving the implementation of the action plan, with a relatively small range of 7.9-8.6 and an average SD of 1.6 between the recommendations. The average mean relevance score was 8.2 (Figure 7).

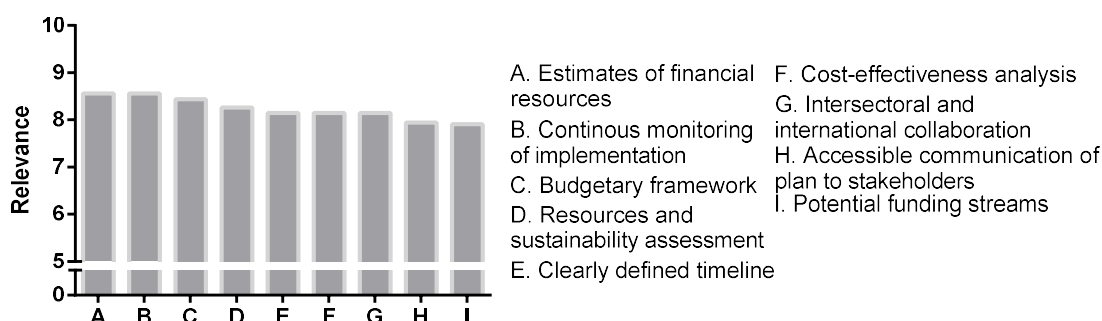


Figure 7. Recommendations for implementing a sustainable national action plan. 33 respondents scored recommendations based on relevance. Each recommendation was evaluated on a scale of 1-10 based on relevance of implementation and addition of recommendation into the PRAN 2014-2018 within the current Spanish context. Results are represented as mean scores

ECDC country visit to Spain recommendations for improving national strategy

Mean relevance score for each person in the ECDC recommendations categories was 8.64 (Range=5.92-9.86; SD: 0.88) with the mean SD of each respondent 1.03 (Range=0.27-2.28, SD=0.47). 58% of respondents had an SD below 1.1, indicating very low discriminatory power (only selected 2 or 3 values). The SD in the table represents the variability between respondents (Supplementary Table 8).

The experts gave a small range of relevance scores between the recommendations for improving the implementation of the action plan, with a relatively small range of 8.1-9.1 and an average SD of 1.4 between the recommendations. The average mean relevance score was 8.6 (Figure 8), scoring slightly higher on average than recommendation proposed for an implementation plan (Figure 7).

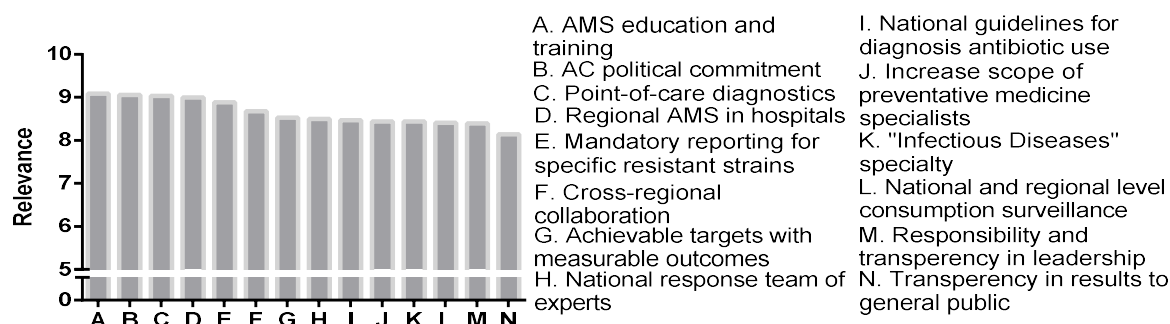


Figure 8. ECDC Spain country visit to discuss antimicrobial resistance issues final recommendations. 33 respondents scored recommendations based on relevance. Each recommendation was evaluated on a scale of 1-10 based on relevance of implementation and addition of recommendation into the PRAN 2014-2018 within the current Spanish context. Results are represented as mean scores.

When asked about the feasibility of implementation of these recommendations, 79% did not provide additional comments. The consensus was that although these recommendations are feasible in the Spanish context (with one respondent indicating some of these are already implemented in Spain), the main concern was political responsibility, coordination, and indecision in actions. Furthermore, one respondent specifically mentioned the importance of a recognized infectious disease specialists playing an active role in the national committee of experts. It is important to note that in Spain currently, infectious diseases is not recognized as a specialty in the field of medicine. Recognition of this specialty was mentioned as a key step in expanding the scope and improving implementation of the PRAN in the previous section.

Questionnaire responses by profession

Respondents were also grouped by profession. Results in the graphs below are presented by 4 of the major professions of respondents, based on responses by participating as to their field of expertise. Only professions represented by more than 5 respondents were compared (Project manager and epidemiologists were represented by 1 respondent each and thus omitted from this analysis).

In overall responses to barriers, veterinarians had the lowest total mean of responses at 5.5. The other strata had similar response averages ranging from 7.5-8 with physicians having the highest mean response. Standard error of the means (SEM) all fell at 0.1, indicating low distinguishability of relevance between barriers by profession. Average SD between respondents for each barrier by profession ranged between 1.7 – 2.0 indicating high variability by profession in response to each barrier (Figure 9).

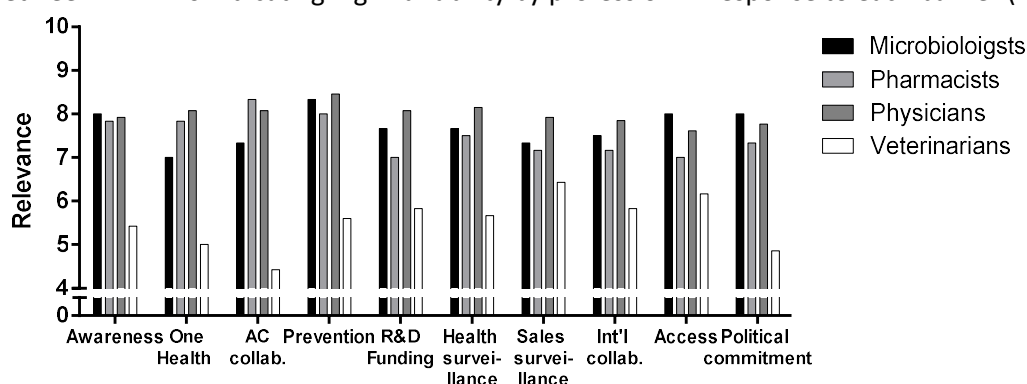


Figure 9. Barriers to fighting AMR in Spanish context. 31 respondents scored barriers on scale of 1-10 based on relevance, with higher score indicating higher relevance. Respondents were stratified by profession Mean score for each barrier was calculated.

In responses to priorities of proposed actions for expanding the scope of the PRAN and improve implementation, the lowest priorities by profession were “multisectoral one health approach” (for pharmacologists/pharmacists, and microbiologists) “effectiveness research” (physicians) and “multifaceted approach to promotion and education of appropriate use of antimicrobials” and “R&D in new treatments and incentives for industries to invest in AMR research” (veterinarians). “Development, improvement, and implementation of point-of-care diagnostics” was the top priority in 3 of the 4 strata, with physicians ranking “improvement in scope and implementation of antimicrobial stewardship and infection prevention” as their highest priority. The mean priority scores by profession fell within the range of 8.3-8.9. Highest priority actions were generally met with a good consensus among responses, represented by a low SD of mean responses. SEM of mean scores fell at 0.2, indicating low distinguishability of relevance between barriers by profession (Figure 10A).

In evaluating feasibility of introducing these actions to improve the scope and implementation of the PRAN, the actions seen as most feasible by each profession were “stronger surveillance of infections, treatment, and antibiotic consumption” (microbiologists and pharmacists/pharmacologists), “increasing the use of point-of-care diagnostic tools” (physicians), and “developing a regulatory framework on prudent use of antibiotics and medicated feed” (veterinarians). The actions receiving the lowest feasibility scores by profession included “multisectoral commitment to prevention and control” (microbiologists, pharmacists/pharmacologists, physicians) and “intersectoral coordination in research and surveillance at all levels of governance including local, regional, and national” (veterinarians). The

mean response scores between the professions ranged 6.6-7.6, with pharmacists/pharmacologists giving the lowest mean scores and physicians the highest mean scores. SEM of mean scores fell around 0.2 for 3 professions with pharmacists/pharmacologists mean scores having and SEM of 0.34, indicating higher level of distinguishability between interventions (Figure 10B).

In comparing potential impact of actions proposed, “improving point-of-care diagnostics” was the most impactful in the short term. However, microbiologists saw all the interventions as impactful in the long term, with all 10 actions averaging above 8.5. Pharmacists/pharmacologists scored “improving surveillance in infections, treatment, and antibiotic consumption” as being the most impactful in the short term and in the long term, along with great long-term benefits from “antimicrobial stewardship” and “development and implementation of better diagnostic tools and practices”. Veterinarians scored “development of a regulatory framework for prudent use of antibiotics in animals, stewardship” and “prevention, and improving point-of-care diagnostics” as the most impactful actions in the short term. Veterinarians scored the same actions as the highest priority in the long term while also adding the “R&D in antimicrobials and incentives for increasing industry involvement”. Long-term impact of actions scored higher on average across all professions. The SEM of the actions’ short-term impact scores of microbiologists and pharmacologists/pharmacists was higher (0.35 and 0.33, respectively) compared to that of the physicians and veterinarians (0.22 and 0.17, respectively). Pharmacists/pharmacologists had on average the lowest short term and long-term impact scores of all the professions (Figure 10).

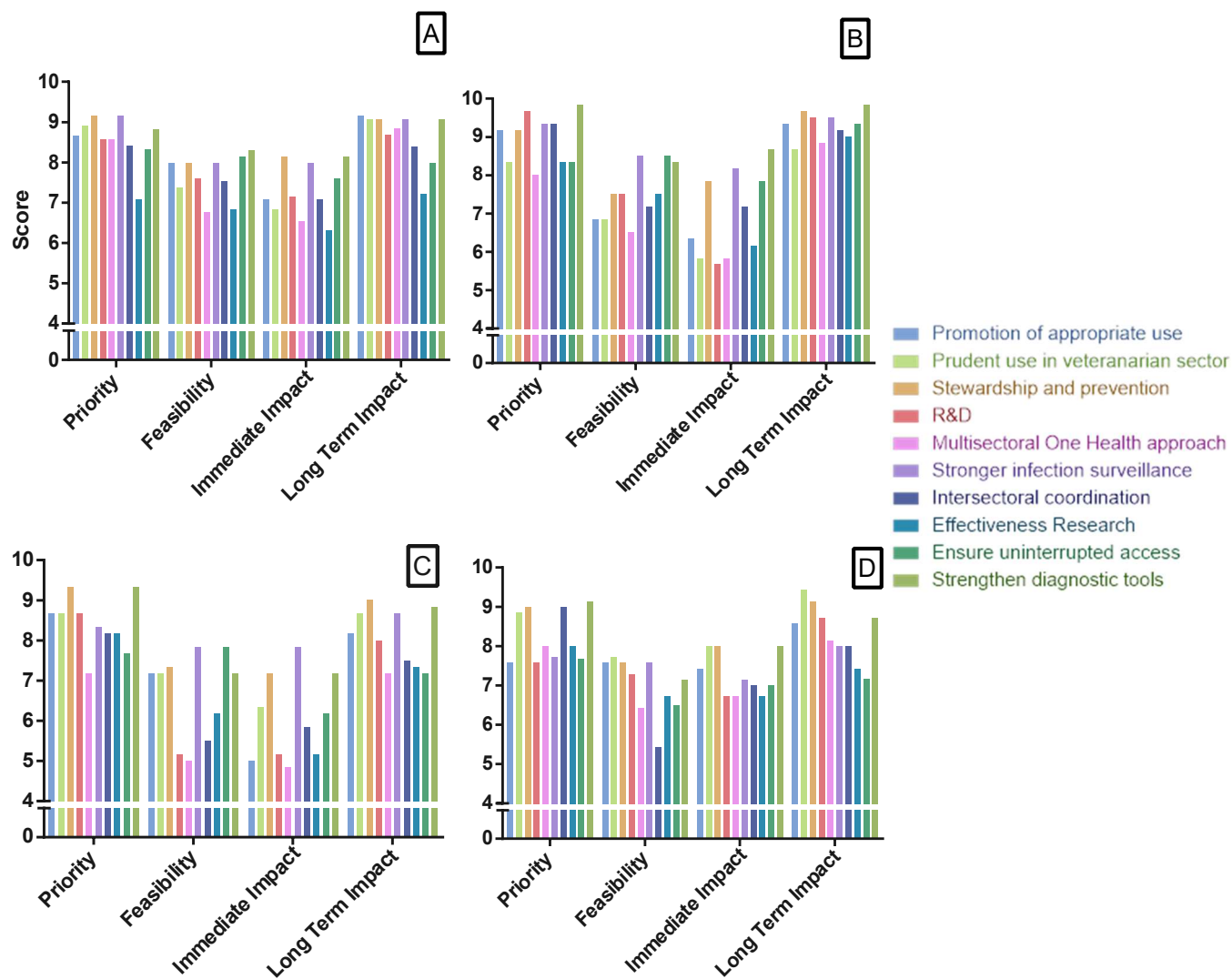


Figure 10. Action in expanding scope and implementation of PRAN 2014-2018, by profession. 31 respondents scored proposed actions on a scale of 1-10 based on priority, feasibility, potential immediate impact, and potential long-term impact with higher score indicating higher priority, feasibility, and impact, respectively. Respondents were stratified by profession: microbiologists (A), pharmacists (B), physicians (C), and veterinarians (D). Mean score for each action was calculated.

4. Discussion

In this study, PRAN was mapped according to EU and WHO action plans, guidelines, and recommendations to identify strengths and weaknesses of the Spanish NAP. Mapping these policies identified key weaknesses and barriers not addressed in the actions. Furthermore, a lack of an implementation plan, budgetary plan, timeline, and M&E plan in the NAP were identified as barriers to effective implementation of the plan. Moreover, details regarding responsibility and oversight over action implementation, as well as any means of collaboration and implementation in Spain's Autonomous Communities (in Spain's health system, each Autonomous Community is in charge of its own budget and health system), also acts as a major barrier in implementation of a national action plan, as stated by the EPHA[22]. Recommendations made based on mapping the Spanish policy, as well as

comparing it with other action plans, reports, and studies, were presented to expert stakeholders to positive reviews.

4.1 Policy Mapping PRAN 2014-2018

PRAN's general objectives cites its development as a fulfillment of the European Commission's Communication of November 17, 2011, establishing an *Action plan against the rising threats from Antimicrobial Resistance* [12] request to MS to prepare a NAP on AMR. The PRAN also cited the 11 aspects listed in point 29 of EU Council Communication of June 22, 2012 *Council conclusions on the impact of antimicrobial resistance in the human health sector and in the veterinary sector – a "One Health" perspective*[21] as a basis for pursuing a One Health approach. Therefore, these documents were selected as key guidelines for mapping the PRAN.

Similar focus on surveillance was observed in both the Spanish and European plans. Actions in surveillance in both plans combine strengthening surveillance efforts in both animal as well as health sectors. Surveillance mentioned in plans are thorough, including surveillance of AMR infections and antibiotic sales, prescriptions, and consumption. The PRAN even designated one of its strategic lines to surveillance of antibiotic consumption and resistance. Another very important aspect of surveillance is the ability for researchers and professionals to access and analyse the data. Both plans have specific actions to increase access to surveillance data and expand analysis (PRAN measure I.1; EU action plan action #1) [12, 13]. The EU action plan mentions collaboration with agencies such as the ECDC along with MS to strengthen surveillance and analysis of data. However, the PRAN does not provide any detail as to who will be held accountable for implementing and strengthening new and existing surveillance infrastructure and how stronger surveillance will be evaluated (i.e. mentioning targets of indicators or specific goals for improved surveillance). It is important to note that one example of significant improvement in surveillance since the implementation of the PRAN in 2014 is Spain's collection and reporting of national consumption of antimicrobials for systemic use in the hospital sector to the ECDC starting in 2017 [16].

Infection prevention was also given similar attention in both plans. However, at 9% of actions in PRAN and 10% in the EU action plan, these make up very small proportions of both action plans (Figure 1). Although the EU action plan includes "Prevent microbial infections and their spread" as an aim and the PRAN includes "control bacterial resistance" as a strategic line, these plans only provide 4 and 7 actions, respectively, directly addressing infection prevention [12, 13]. However, the strategic line in PRAN addresses the issue of controlling resistant infections through other actions, principally through AMR stewardship, making up 9 of the 15 actions in this strategic line and 28% of the total actions in the plan, as well as R&D. As a matter of fact, antimicrobial stewardship made up the largest category and focus of the PRAN (Figure 1). The EU plan puts a heavier emphasis on R&D, as it indicates that one of its key aims is to improve collaboration in R&D among MS as well as coordinating with other international actors such as the WHO or Codex Alimentarius[12]. This focus helps to explain the EU action plan's strong emphasis on multilateral collaboration and R&D, making up a combined 46% of the actions proposed. Although the design of the PRAN incorporates the intersectoral component of a One Health approach by indicating actions specific to the health sector and animal sector (mainly independently), there is a gap

in addressing collaborative intersectoral interventions that bring together the health sector, animal sectors and other sectors (e.g. environmental sector).

As a NAP, there is a strong focus on improving public awareness as well as education and training of professionals and key stakeholders in the PRAN, making up 2 of the 6 strategic lines of the plan. The plan looks to combine population wide approaches as well as targeting key population subgroups to improve awareness and knowledge on AMR [13]. However, as shown by the Eurobarometer 2018 special report on AMR, knowledge in Spain saw a minimal improvement since 2016 in general AMR knowledge questions answered correctly, falling below the EU MS average [17].

Although many key differences in focus have been noted between the EU action plan and PRAN, it is important to note the difference in scope and roles these documents and their authors play in controlling AMR. The European action plan was aimed at strengthening existing international initiatives and empowering programs in MS to invest, collaborate and develop their own individual plan[12]. The PRAN was made with specificities to the Spanish context, and therefore the focus and specific actions drawn up will reflect the context in which it was to be implemented in[13].

To analyse breadth and adherence to the One Health approach proposed by the EU Council communication of June 22, 2012, a checklist of the 12 aspects listed under point 29 “Calls [to] the Member States”, was made to evaluate breadth and adherence in animal sector and health sector to aspects mentioned (Table 1). One of the aspects neglected by the PRAN was the limiting of use of antimicrobials for herd treatment of animals to cases assessed by veterinarians and justified by epidemiological data. This, however, is addressed indirectly in the PRAN by actions that limit use of antimicrobials in ways that differ from those authorised and developing guidelines pertaining to exceptional prescription of antibiotics (measures II.2 and II.3). As a matter of fact, Spain’s NAP mentions several ways in which guidelines in human and animal sectors must be implemented to better regulate and monitor the use of antibiotics, prescription in extraordinary situations, and restricted use of critically important antimicrobials. However, Spain’s plan and the European plan failed to provide actions to control illegal use of antimicrobials or use without a prescription. This is reflected in the Eurobarometer 2018 special report on AMR, in which 5% of respondents from Spain and 7% from the EU have taken antibiotics in the previous year without a prescription, the same as in 2016[17].

Although all actions in the Spanish NAP are divided into health sector, animal sector, or both sectors, further information must be provided to specify which stakeholders are to be made responsible for carrying out the actions, their implementation, and their monitoring. Furthermore, other sectors and stakeholders apart from health, animal, and agriculture sectors, such as the financial sector, environmental sector, and business sector (i.e. industry) must be more deeply incorporated in the PRAN as their responsibilities and potential affect in controlling AMR could prove to be beneficial to improving the scope and implementation of the Spanish NAP.

4.2 Multilateral cooperation, Intersectoral collaboration, and Implementation

The WHO’s Global Action Plan (2015) to combat AMR and the EU’s European One Health Action Plan against AMR (2017) put great emphasis on promoting and supporting international collaboration among

MS in research, surveillance, and raising awareness [23, 26]. Keeping in line with the European One Health Action Plan's pillar to make Europe a "best practice region", EU-Joint Action Antimicrobial Resistance and Health-Associated Infections (EU-JAMRAI) is a collaboration that was created with the mission to bring together MS and international governance bodies and stakeholders to improve implementation of evidence-based interventions tackling AMR. Of their 9 work packages aimed at addressing their main goal of bringing EU level cooperation to improve national AMR-related policies, Spain, represented by AEMPS, is leading 3 work packages (Figure 11)[27]. Furthermore, Spain is a collaborator on Work Package 5, participating in a pilot of the Country-to-Country visits initiative. Spain and the AEMPS hosted a Dutch delegation in November 2018, to pilot a peer review system in which countries evaluate each other's national action plan and trade ideas on policies and implementation [28]. Spain is scheduled to send a delegation to Sweden in October 2019.

Consistency between the objectives of WHO, EU and the JA Work Packages

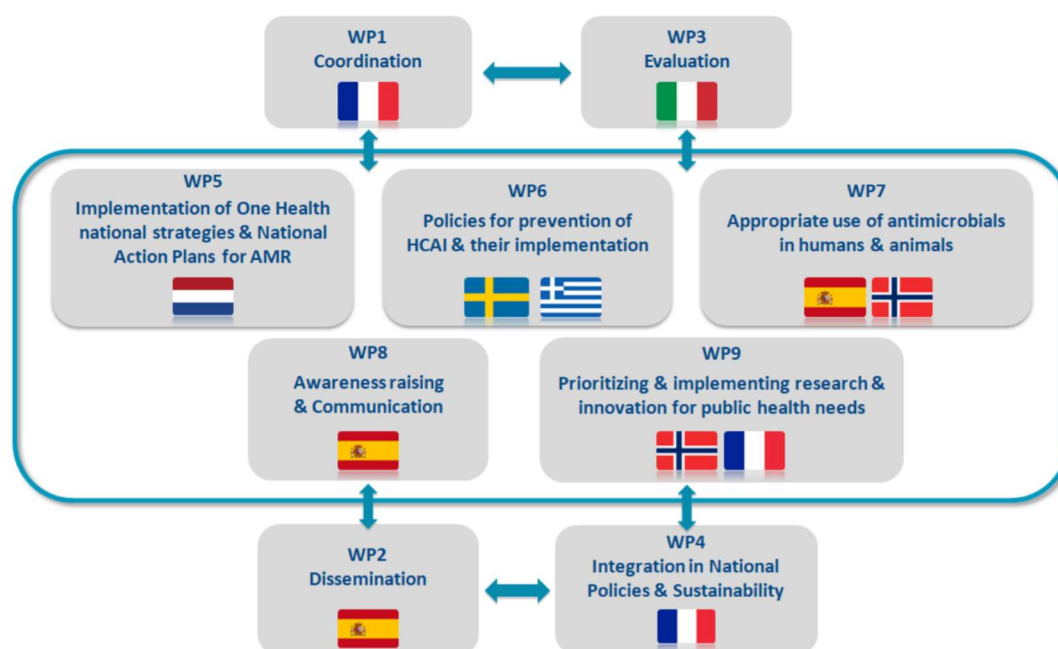


Figure 11. An update on the results of the Joint Action after 18 months of implementation: Consistency between the objectives of WHO, EU, and the JA Work Packages. From: EU-JAMRAI (2019)[27]

In the EPHA's 2018 report "Translating political Commitments into action: The development and implementation of National Action Plans on antimicrobial resistance in Europe", available NAP on AMR from all EU/EEA MS were compiled and analysed in a framework to evaluate the development and implementation of NAP in Europe. The framework used covers 4 thematic areas, including:

1. One health Approach
2. Financing estimates and identification of financing streams
3. Integrating implementation and evaluation mechanisms
4. Identifying clear measurable goals

The PRAN only partially fulfills the One Health approach. The EPHA classifies the PRAN as a: “National action plan with a One Health focus, covering specific actions on human, animal health, and foodborne AMR and agriculture”. Although Spain addresses these aspects of a One Health approach thoroughly, Spain’s plan does not specify the manner in which collaboration of actors from multiple sectors will be facilitated to accomplish objectives and fulfill activities[22].

Furthermore, the environmental dimension of the One Health perspective is neglected. This dimension, as is pointed out in the EPHA report, is often neglected in NAP across Europe, with only 2 MS shown to introduce specific actions addressing the environmental dimension of AMR [22]. The principle of incorporating the environmental sector into NAP to combat AMR is one that has been found throughout action plans, recommendations, and guidelines [12, 22, 23, 26].

The PRAN does not lay out any financial estimates, specify any dedicated funds available, identify financing streams, or include any budgetary framework. The EPHA reports this as a common shortcoming in NAP across Europe. However, there are some NAP that do address this component. One example of this is the UK strategy which includes a detailed Impact Assessment. This impact assessment identifies cost estimates, and cost-benefit of implementing actions in key strategic areas. Furthermore, the strategy assesses impact of implementing strategies versus inaction [22, 29].

The PRAN does not include a timeline or implementation plan as is recommended by the Global Action Plan [23]. It does however indicate an annual assessment report presenting results to be used for adjusting the national strategy, actions, and interventions to improve implementation and targeting of key objectives. Nevertheless, the actors responsible for collecting the data, publishing the assessment report, and the dissemination plan is not clear. The PRAN does indicate the creation of work groups to address each measure. These groups are made up of representatives from each Autonomous Community and representatives from ministries, scientific societies, collegiate and professional associations. Furthermore, these groups are tasked with assessing data and assessing current state of achieving the respective measures, propose and design strategies to improve implementation, prepare timelines, implementation plan, designate responsible parties and design measurable targets[13].

4.3 Expert Opinions on Barriers and Recommendations

The main objective of the questionnaire was to get a broad perspective of the findings and recommendations proposed. To do this, experts in the field of AMR were selected based on diversity of 2 characteristics: geographical and professional. As the analysis of the demographics of respondents shows, 10 of the 17 Autonomous Communities across Spain were represented. Furthermore, responses from the healthcare sector (hospital and community) and animal sector were represented along with microbiologists, pharmacologists, pharmacists, epidemiologists, and a project manager in public health. Because Spain’s national health system is divided into 17 regional systems of the Autonomous Communities, a barrier to implementation of an intersectoral NAP according to the EPHA [22], it was important to bring together voices from a wide range of experts in different social, economical and political contexts. Furthermore, because of the intersectoral One Health approach, opinions of professionals with a wide range of experience was sought after to gather information from a broad range of actors.

The range of the means of responses to the barriers of implementation in Spain was less than 1 point (Figure 5) indicating, overall, all of the barriers proposed were interpreted to be of similar relevance. However, it is difficult to interpret the order of relevance based on the responses because the range is narrow and variability in responses was high (supplementary table 2). When experts were asked to mention additional barriers they saw as relevant in the Spanish context, their responses fell into 5 categories: 1) awareness, 2) education and training, 3) coordination and conflict between stakeholders and their interests, 4) enforcement of regulation of prescription and dispensing, and 5) political and financial commitment. These responses corroborate the findings of the policy mapping as well as findings from the Eurobarometer 2018 and EPHA [17, 22]. Specifically, the lack of budget and public funding was of concern to several respondents and seems to be a major barrier in addressing AMR. Of interest was the inclusion of pressures on physicians to prescribe antibiotics. Although the pressures weren't specified, one study showed that pressures from patient expectations and the pharmaceutical industries to inappropriately prescribe antibiotics plays a role in misuse of antibiotics and increases the risk of AMR dissemination. This paper goes on to cite lack of knowledge, education, and training amongst physicians and patients as contributing factors to the rise of these pressures [30]. Therefore, psychological factors that lead to overprescribing also pose a potential barrier and must be studied further.

When asked about locally implemented interventions to address AMR, many respondents mentioned the Programs to Optimize the Use of Antibiotics in hospitals (PROA). Based on pre-existing Autonomous Community run programs such as the PIRASOA in Andalusia or VINCAT in Catalonia, the PROA are national level programs of antimicrobial stewardship and surveillance, providing guidelines for regional level coordination and local implementation. The PROA model requires a collaboration between national and regional level coordination for implementation in hospitals as well as primary care centres, with locally implemented PROA showing efficacy in reducing antibiotic consumption[31, 32]. Other interventions mentioned were research efforts, improving guidelines for diagnosis, and improving implementation of good practice in the animal sector.

In general, mean scores of the actions proposed, measured on 4 axes, was not wide (between 1.4 and 1.8), making detection of trends, priorities, or weaknesses to be addressed difficult to point out distinctly. However, within the narrow range 2 actions did stand out: AMR stewardship, tracking of transmission in the environment and preventative actions (i.e. increasing vaccine arsenal and coverage), and further promoting prudent use of AMR and developing and strengthening use of point-of-care diagnostic tools (Figure 6).

An interesting trend that did emerge is the difference in scoring between the 4 axes of measurement. Immediate impact and feasibility seemed to consistently rank lower than priority and long-term impact across the different actions (Figure 6). This may indicate a consensus that AMR interventions are recognized as being of high priority with a high potential long-term impact. Nevertheless, the feasibility of implementation of these interventions is difficult due to present barriers described previously. Furthermore, the relatively low immediate impact compared to long term impact may be seen as a barrier to implementation, acceptability and sustainability of interventions.

Asked about additional actions to expand scope and implementation of PRAN, respondents mentioned 4 possible dimensions: 1) Expanding One Health scope to include more sectors/intersectoral coordination, 2) outreach campaigns and interventions in population, 3) training and education programs, and 4) R&D in alternative antimicrobial treatments. These findings corroborate findings from mapping of the PRAN, with focus on multisectoral coordination being the weakest focus in the plan (Figure 1). Poor implementation of training and education programs is reflected by results of the Eurobarometer, showing minimal changes in public awareness and knowledge regarding AMR [17]. Furthermore, increasing the scope of professional training of healthcare professionals and other important actors to include AMR was also mentioned, with the inclusion of infectious diseases as a recognized specialization in Spain presented repeatedly.

The recommendations scored in a narrow range and in a consistent range between the sets of recommendations (Recommendations made from policy mapping and ECDC country visit to Spain recommendations; Figure 7 and 8). It appears that both recommendations were received equally by respondents as scores fell in a similar range. Nevertheless, due to the narrow range of means of responses, it is difficult to compare and rank acceptance of recommendations.

When asked about the feasibility of implementing these recommendations, the responses focused on the composition of a national committee and collaboration between Autonomous Communities. Respondents referenced political commitment as a major hurdle. Furthermore, for stronger implementation in the Autonomous Communities, a centralised committee made up of representatives from all of the Autonomous Communities was seen as a priority. As mentioned previously, the plan is divided into measures, each of which has an independent subgroup consisting of representatives from the Autonomous Communities[13], however, there is no mention of a general centralised committee responsible and accountable for implementation of measures at the local level. The composition of experts that make up a central committee was also referenced, indicating the importance of including recognized infectious disease experts in the committee.

The opinions of experts by profession were also graphed in order to better understand how the field of expertise affects priorities and opinions on barriers and interventions in a One Health plan. The data shows much larger variation amongst professions as well as by professions. For example, among the barriers, veterinarians consistently ranked every option lower, than every other professional background (Figure 9). Therefore, comparing relevance between professions (e.g. relevance of One Health Approach to veterinarians versus microbiologists) would not provide a valid comparison. However, comparing the different barriers within each profession indicates areas of focus in the different fields.

Among the professions, microbiologists and physicians ranked infection prevention as the most relevant barrier in Spain, where as pharmacologists also ranked infection prevention as the second most relevant barrier. Veterinarians scored infection prevention relatively low compared to consumption surveillance (Figure 9). According to ECDC data on consumption of antimicrobials for agriculture use, Spain consumes far beyond the EU average[18], and thus, its consumption and regulation of sales are an important intervention in controlling the spread of AMR in Spain. Of note is the difference in opinion on the effect of interregional collaboration by veterinarians, who ranked it as the least relevant barrier, compared to

pharmacists and physicians who ranked it as the first and second most relevant barrier, respectively (Figure 9). Nevertheless, it is important to note that the range of responses within the fields of expertise was quite narrow with substantial variability, therefore it is difficult to conclude whether there is a significant difference in relevance between the barriers.

Results regarding actions to increase the scope and implementation of the PRAN reflect similar results to findings in the overall analysis. One aspect of note is the veterinarians focus on improving prudent use of antimicrobials in the veterinarian sector. This relationship seems natural due to the scope and experience of respondents. Interestingly, whereas veterinarians scored improvement in this intervention as very feasible (when compared to interventions such as intersectoral coordination), microbiologists and pharmacologists ranked it as among the least feasible interventions. The most convincing action to expand the scope and implementation of the PRAN across the 4 axes and across the 4 fields was strengthening implementation and development of point-of-care diagnostics (Figure 10).

4.4 Limitations

Many limitations were encountered in this research. The policy mapping was conducted by a single researcher without a second reviewing researcher, therefore, inter-rater reliability was not tested. In the questionnaire, first, a low sample size means there was low statistical strength to the findings. Second, as the questionnaire was distributed in several networks and spread by snowball effect, a selection bias may be present in the respondents replying to request emails. Third, a low range of responses to scoring items in the questionnaire and high variability made analysing reactions to different interventions and recommendations difficult to distinguish. Fourth, measurement error, or the deviation of answers of the respondents from their true value in the measures used due to an absence of interviewer present to explain any misunderstanding in the questionnaire during a self-administration[33] can not be ruled out. Fifth, the study must be replicated with additional samples for external validity. Finally, situational factors, such as time of and day of completion of questionnaire, may affect respondents' interpretation of questionnaire.

4.5 Barriers & Recommendations

Full list of barriers identified in mapping of PRAN and from expert responses:

- Public awareness and education on AMR (evaluating and improving accessibility of public to knowledge, education, and information)
- Collaboration in a true “One Health” approach: seamlessly incorporating human and animal health in all actions and strategies as well as including non-traditional ‘one health’ aspects such as the environment and use of antimicrobials in agriculture
- Collaboration and political commitment between the Autonomous Communities at the national and local levels
- Infection control and prevention in the community and hospitals
- Funding towards R&D in antimicrobials, treatment alternatives, prevention, and diagnostics
- Development of a strong and cohesive local and national surveillance network at primary care and hospitals settings
- Monitoring, surveillance, and oversight of the consumption of antimicrobials and rate of AMR infection in farming and agriculture

- Bilateral and multilateral collaboration by Spain and Spanish stakeholders at an international level (i.e. with international organizations and other states)
- Consistent access to medicine and high quality healthcare
- Commitment of funding and resources from public institutions, professional societies, and government
- Spread of misinformation,
- Slow implementation of diagnostic procedures in primary health consultations
- Inadequate training of professionals on the appropriate use and consequences of inappropriate use of antimicrobials.
- Lack of regulation on prescription and dispensing practices leading to potential conflict of interests
- Pressures for prescribing from patients and pharmaceutical industry

Recommendations for improving implementation of PRAN:

- Assessment of resources needed and sustainability of interventions
- Timeline with clearly defined incremental targets for achieving specified objectives that are: Specific, Measurable, Achievable, Relevant, and Time-bound
- Estimates of required financial resources for each action
- Source of funding and potential funding streams for each action
- Fitting AMR budgets into a budgetary framework
- Cost-effectiveness analysis of individual actions and the National Action Plan compared to inaction
- Monitoring of implementation of actions, effectiveness of plan, and delivery of services on a continuous basis
- Bilateral and multilateral collaboration between Spain and other relevant Spanish actors at the international level (e.g. with other states or international organisations).
- Accessible communication of the plan, its scope, actions, and the progress made between the governing body and professional stakeholders as well as the public (i.e. through a website, social networks, etc.)

Full list of recommendations from the ECDC country-visit to Spain to discuss AMR can be found in the report[14].

5. Conclusions

In conclusion, the Spanish NAP on AMR for the years 2014-2018 was mapped according to the AMR action plan published by the European Council and guidelines for One Health approach in AMR policies to establish breadth of actions and adherence to a One Health approach. Strengths of the Spanish plan as well as weaknesses and barriers to implementation were identified. Using the WHO Global Action Plan and documents from other international organizations such as the EU and EPHA, further actions to expand the scope of the PRAN by identifying aspects missing from the plan were compiled. Furthermore, due to the lack of measurable targets or an implementation plan, actions and recommendations for improving the implementation of measures in the PRAN were proposed. These were compiled and given to stakeholders from different fields of expertise working in 10 different Autonomous Communities across Spain in the form of an online questionnaire. Results did not provide

much of a hierarchy of relevance and priority in barriers and interventions. However, improving development and use of point-of-care diagnostic tools and improving implementation of antimicrobial stewardship and infection prevention interventions were selected overall to be high priority interventions requiring improved implementation. Furthermore, improved implementation was seen to be most feasible, with high potential immediate and long-term impact. When data was categorized by profession of respondents, some responses were shown to lean towards interventions in the expert's field. For example, veterinarians ranked implementation of guidelines for prudent use of antibiotics in the veterinarian sector as a very high priority, very feasible, and having high potential immediate and short-term impact, compared to professionals in other fields.

Outcomes of questions in relevance of recommendations were not analysed by profession due to the nature of the recommendations. As recommendations made based on policy mapping of the PRAN were focused on implementation framework, financing, and budgetary planning, the conception of individuals based on professional background was not seen as relevant. Furthermore, as the ECDC country visit to Spain was primarily focused on prudent use of antimicrobials and antimicrobial stewardship, the recommendations are mainly addressed to the human health sector and did not take a broad One Health approach to the investigation. Nevertheless, conclusions and recommendations did point out Spain's strength in incorporating animal and human health sectors in the NAP. Some recommendations focused on strengthening the intersectoral collaboration, such as the development of an Intersectoral Coordinating Mechanism [14].

Further steps to improve the understanding of the current state of AMR control in Spain is to re-administer a questionnaire with a greater sample size. This would allow for statistical inference. Furthermore, gaining larger samples from individual Autonomous Communities would allow for a comparison between regions to understand how priorities are aligned with each other and with the NAP. Furthermore, structured interviews with experts in the field must be conducted to gain deeper insight into conceptions of the state of implementation of the PRAN and its organization. Finally, due to methodology being established in late 2018 and a cut off point was placed for documents used in mapping and analyzing the PRAN. Therefore, the updated PRAN 2019-2021[34] was not included in the analysis. Nevertheless, it is important to conduct additional mapping of the 2019 Spanish NAP to identify its strengths and weaknesses.

Findings from this study as well as interviews directed to key leaders and selected experts in the field and further investigations can be used to assess progress made with the new plan and corroborate whether changes and updates made are aligned with the needs and observations of experts and a reflection of a step in the right direction for Spain in the fight to control AMR. Furthermore, comparing policy mapping of the old and new PRAN could provide analysis of progress made, and allow us to better understand whether weaknesses have been addressed and provide evidence that the new NAP built on existing the strengths of the PRAN.

The PRAN 2014-2018 was a major step in the fight against the dissemination of AMR in Spain and a major political gesture in showing national commitment to the global fight. It is crucial for Spain to continue collaborating locally, nationally, and internationally to build on current knowledge, introduce

and implement evidence-based policies, and cooperate with other MS and nations to build a united front against the rising threat of AMR.

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Annex 1: Questionnaire

The questionnaire in English can be accessed via the link below:

English:

<https://docs.google.com/forms/d/e/1FAIpQLSdExO9OuRiR02inEwyu0vCK4HAWRfrWYwMttCxEO7IGBL0Gw/viewform>

Spanish:

https://docs.google.com/forms/d/e/1FAIpQLSc4YPSSMyiX3pLMqf9EC2plaT2WHBt1u_dYKou2wHvxKZxcXA/viewform

Annex 2: Tables

Supplementary Table 1. List of questionnaire respondents and institutions they are involved with

NAME	INSTITUTION
José Antonio Oteo	Hospital U. San Pedro
Rafael Canton	Hospital Ramón y Cajal. Madrid. España
Jerónimo Pachón Díaz	Instituto de Biomedicina de Sevilla
Younes Smani	Instituto de Biomedicina de Sevilla
Ángel Rodríguez Villodres	Hospital Universitario Virgen del Rocío
Cecilia	HUVR
Francisco Alvarez Lerma	Hospital del Mar
Anonymous	Instituto Ncl. Investigación y Tecnología Agraria y Alimentaria
Angel Asensio	Sociedad española de Medicina Preventiva y Salud Pública
Anonymous	Instituto Aragonés de Salud
Anonymous	Universidad Complutense
Carles Cristòfol	çservei d'Anàlisi de Fàrmacs
José Miguel Mejias Montalbo	SEOC
Jordi Vila	Hospital Clinic
Carmen Alaez	Fundacion Tecnología y Salud
Concepcion Caballero Galván	Unidad de Análisis Sanidad Animal. Generalitat Valenciana
Anonymous	ICS
Anonymous	MAPA
Amapola	Fundación Tecnología y Salud
LUIS MIGUEL CEBRIÁN YAGÜE	
Margarita Arboix	Universidad Autónoma de Barcelona
Anonymous	Hospital Universitari Son Espases

M. Carmen Fariñas	Hospital Universitario Marqués de Valdecilla
Marta Fernández Martínez	Hosp Univ Marqués de Valdecilla /IDIVAL/ REIPI
Albert	Institut Català de la Salut
Juan Pablo Horcajada	Hospital del Mar. Barcelona
Anonymous	Hospital Clinico Universitario de Valladolid
Anonymous	AESAN
Amós José García Rojas	Servicio de Epidemiología y Prevención. DGSP Canarias. Presidente de la Asociación Española de Vacunología
juan grandia	agro-test control
Pablo Rojo	Hospital 12 de Octubre
Anonymous	VISAVET-UCM
Jesús Rodríguez Baño	Hospital Universitario Virgen Macarena

Supplementary Table 2. Barriers to fighting AMR in Spanish context. 33 respondents scored barriers on scale of 1-10 based on relevance, with higher score indicating higher relevance. Mean score for each barrier was calculated with Standard Deviation.

Barriers	Relevance	SD
Public awareness and education	7.352941	2.1
"One Health" approach and collaboration	7.117647	2.4
Collaboration and commitment of AC	7.117647	2.4
Infection control and prevention in community and hospitals	7.8125	1.7
R&D Funding	7.151515	2.4
Surveillance network in hospitals and primary care centres	7.454545	1.9
Surveillance and monitoring of antibiotic consumption	7.323529	1.8
Spanish collaboration with external actors	7.242424	1.8
Access to high quality medicine and treatment	7.121212	1.9
Political and financial commitment	7.117647	2.4

Supplementary Table 3. Actions to expand the scope and improve implementation of the PRAN. 33 respondents scored proposed actions based on 4 criteria: priority of introducing action to improve scope and implementation of PRAN, feasibility of introduction, immediate impact, and long-term impact. Each criterium was evaluated on a scale of 1-10, with higher scores indicating better outcome under respective criterium. Results are represented as mean of responses and standard deviation.

New actions/Needing improved implementation	Priority	SD	Feasibility	SD	Immediate Impact	SD	Long-term Impact	SD
Increase promotion and awareness of appropriate use of antimicrobials	8.558824	1.501336	7.470588	1.236694	6.705882	1.714986	8.823529	1.140722
Regulatory framework for	8.764706	1.129731	7.264706	1.441986	6.882353	2.04146	8.911765	1.334113

prudent use in animal medicine								
Antimicrobial Stewardship and infection prevention	9.212121	0.892944	7.676471	1.248529	7.911765	1.464068	9.117647	0.769286
R&D	8.647059	1.667558	7.117647	1.665418	6.529412	2.377104	8.676471	1.319334
Better implementation of "One Health" across all involved sectors	8.117647	1.492704	6.411765	1.5786	6.235294	1.875824	8.323529	1.646311
Strengthen surveillance of infection, treatment, and antibiotic consumption	8.764706	1.596565	7.970588	0.968763	7.882353	1.451534	8.823529	1.242446
Co-ordinate research and surveillance efforts on a local, national and international level	8.735294	1.286499	6.676471	1.804382	6.970588	1.976917	8.294118	1.661132
Effectiveness Research	7.823529	1.445381	6.823529	1.358934	6.323529	1.90248	7.647059	1.790249
Ensure uninterrupted access to essential medicines of assured quality	8.060606	1.619016	7.757576	1.4368	7.333333	2.01039	7.969697	1.87891
Development and implementation of better diagnostic tools	9.205882	0.808268	7.764706	1.207522	8.029412	1.641974	9.029412	1.086705

Supplementary Table 4. Recommendations for implementing a sustainable national action plan. 33 respondents scored recommendations based on relevance. Each recommendation was evaluated on a scale of 1-10 based on relevance of implementation and addition of recommendation into the PRAN 2014-2018 within the current Spanish context. Results are represented as mean scores and standard deviation.

Recommendations for improved implementation of NAP	Relevance	SD
Assessment of resources needed and sustainability of interventions	8.264706	1.48342
Timeline with clearly defined incremental targets	8.147059	1.559572
Estimates of required financial resources for each action	8.558824	1.259898
Source of funding and potential funding streams for each action	7.911765	1.583392
Fitting AMR budgets into a budgetary framework	8.441176	1.283725
Cost-effectiveness analysis of individual actions and the National Action Plan compared to inaction	8.147059	1.98681
Monitoring of implementation of actions, effectiveness of plan, and delivery of services on a continuous basis	8.558824	1.374909
collaboration between Spain and other relevant Spanish actors at the international level	8.147059	1.69012
Accessible communication of the plan, its scope, actions, and progress made between the governing body, the professional stakeholders, and the general public	7.941176	1.791244

Supplementary Table 5. ECDC Spain country visit to discuss antimicrobial resistance issues final recommendations. 33 respondents scored recommendations based on relevance. Each recommendation was evaluated on a scale of 1-10 based on relevance of implementation and addition of recommendation

into the PRAN 2014-2018 within the current Spanish context. Results are represented as mean scores and standard deviation.

ECDC recommendations	Relevance	SD
Responsibility and transparency in leadership of each action	8.393939	1.273268
AC political commitment	9.060606	1.344884
Achievable targets with measurable outcomes	8.529412	1.419246
Collaboration and information sharing infrastructure among AC	8.676471	1.491808
Mandatory reporting for specific AMR strains	8.882353	1.297193
National response team of experts	8.5	1.482218
National and regional levels of antibiotic consumption	8.411765	1.519921
Include AMR stewardship in contracts between AC and hospitals	9	1.198958
Make affordable point-of-care diagnostics	9.029412	1.141113
National guidelines for diagnosis antibiotic use	8.470588	1.186676
AMR stewardship in education and training	9.088235	0.933149
Increase scope of preventative medicine specialists and scale up	8.441176	1.481015
Recognize infectious diseases as a medical specialty	8.441176	1.778511
Transparency in results and objectives to general public	8.147059	1.479811

Annex 3: Lists

Supplementary List 1. Responses to questionnaire question 2: Based on your experience, is there any additional barrier in the Spanish context that you consider represents a significant threat to the fight against AMR?

Awareness:

- Lack of adequate training of affected professionals, citizens and entrepreneurs on the circumstances of inappropriate use of antimicrobials
- The low level of health education of the population. The slow implementation of diagnostic procedures in primary care consultations.
- health awareness and education
- disinformation

Education and Training:

- Lack of adequate training of affected professionals, citizens and entrepreneurs on the circumstances of inappropriate use of antimicrobials
- Continuous training of health professionals
- health awareness and education
- Absence of Infectious Disease specialty
- Lack of specialty Infectious Diseases. Lack of specific funding for PROA equipment. The lack of priority in university and specialized training for doctors in the adequate use of antibiotics.
- The low level of health education of the population. The slow implementation of diagnostic procedures in primary care consultations.

- The lack of Specialty Infectious Diseases in Spain and the lukewarmness with which its possible creation is approached. The scarce economic endowment to the PRAN and the scarce contribution of [Spain] to the JPMR in comparison with other European countries.

Coordination and conflicts between stakeholders and interests:

- Conflicts between specialties
- Lack of coordination and
- Competencies divided into 2 Ministries of Agriculture and Health. Animal health from a "one health" point of view should be the responsibility of the Ministry of Health. In the case of companion animals, especially since they are not in agriculture that only deals with production animals.
- Multidisciplinary work under the umbrella of health and public-private collaboration
- some sectors of the food chain where there is a lot of manual handling of food (slaughterhouses, local products...
- Lack of integration between policies affecting human and veterinary medicine

Regulation of prescription and dispensing:

- Pressures for the use of antimicrobials
- Non-compliance with the guarantee of independence in the dispensing of veterinary medicines: reverse prescribing and the provision of clinical services by companies or entities that own dispensing centres.
- Ease in prescribing antibiotics for all doctors

Political and financial commitment:

- The responsibility of the autonomous communities for health
- Lack of financial resources to carry out development plans and scientific research in this framework
- Lack of specific budget
- Funding for implementation of AMR measures
- Lack of public funding and therefore of conviction in decision-makers
- In some areas there is a lack of resources, both in terms of budgets and human resources, to carry out certain important actions.
- Lack of specialty Infectious Diseases. Lack of specific funding for PROA equipment. The lack of priority in university and specialized training for doctors in the adequate use of antibiotics.
- The lack of Specialty Infectious Diseases in Spain and the lukewarmness with which its possible creation is approached. The scarce economic endowment to the PRAN and the scarce contribution of [Spain] to the JPMR in comparison with other European countries.

Supplementary List 2. Responses to questionnaire question 3: Based on your experience, is there any additional barrier in the Spanish context that you consider represents a significant threat to the fight against AMR?

Regional level programs, interventions, and guidelines:

- PROA Programs, National-International Resistance Surveillance Studies

- PRIOAM Program of the Virgen del Rocío University Hospital and PIRASOA Program of Andalusia
- Antimicrobial use optimization programs (PROA)
- Development of the Zero Resistance Project in some Autonomous Communities due to problems of leadership of specialties.
- Implementation of PROA programs in Primary Care with specific sessions for professionals.
- Development of treatment guidelines for the most common processes in each Autonomous Region.
- PROA Programs
- PROA programs have been implemented throughout the Community
- There is a need for greater and better collaboration between different bodies, both official and private, although the PRAN (National Plan for the Control of Antimicrobial Resistances) coordinated by the AEMPS is already being implemented.
- We have a PROA program in the Pediatrics Service on October 12, similar to other Spanish programs, reviewing antimicrobial prescribing and suggesting changes.
- The activity in countries such as Holland and Nordic countries. Activity in the Macarena Hospital with PROA and coordinated infection control equipment.

R&D in antibiotics, alternative antimicrobial treatments, and prevention/vaccines:

- Research on unconventional broad-spectrum antimicrobials. In my own group we investigate unconventional antiviral drugs and active against intracellular bacteria such as Salmonella, etc.. Other groups in the Biotechnology Department of INIA are investigating phage and antibacterial compounds.
- Vaccination against *S. Pneumoniae*

Guidelines for better diagnosis practices:

- Implementation of a common strategy at national level for the use of diagnostic tests in primary care to identify the origin of the infection and the need or not for the use of antibiotics.
- Importance of the implementation of rapid diagnostic tests

Implementing good practices in veterinarians use:

- Campaigns of responsible use and promotion of means of prevention in animal health such as improvement of biosecurity and rational use of adequate and harmonized vaccination protocols at national level in both human and animal health.
- "Collaboration in survey design for pharmacists. Conferences and seminars on drug legislation and good prescribing practice and prescribing veterinarian liability".
- the need to implement good practices
- Raising pigs without antibiotics

Supplementary List 3. Responses to questionnaire question 5: Please indicate any additional actions you deem crucial for developing a National Strategic Action Plan that is in line with a 'One Health' approach to battling AMR in Spain

Expanding one health scope to include more sectors/intersectoral coordination:

- Intersectoral Coordination in Resistance Surveillance and Antimicrobial Development
- Environmental health
- Spread the concept that is everyone's responsibility: users, professionals and administration
- Action at the primary and hospital care level
- To deepen in the multidisciplinary between veterinarians, doctors, laboratories, epidemiologists, sociologists, etc.
- Increase the competencies of the Ministry of Health in Zoonosis, Small Animal Clinic, veterinary prescription control, rigorous control of the use of medicated feeds and the administration of antibiotics to promote growth in animals. Continuous training of health professionals and pharmacists. Well-funded research programmes aimed at finding alternative strategies to antimicrobials and antiviral drugs.

Outreach campaigns and interventions in population:

- set up awareness campaigns at national level with a good audiovisual communication target
- avoid self-medication of the population

Training and education programs:

- Creation of the specialty of Infectious Diseases, as a training tool
- Improve training in clinical pharmacology related to the use of antibiotics by veterinarians.
- Creation of the Specialty of Infectious Diseases in Spain
- Increase the competencies of the Ministry of Health in Zoonosis, Small Animal Clinic, veterinary prescription control, rigorous control of the use of medicated feeds and the administration of antibiotics to promote growth in animals. Continuous training of health professionals and pharmacists. Well-funded research programmes aimed at finding alternative strategies to antimicrobials and antiviral drugs

R&D in treatment alternatives:

- Increase the competencies of the Ministry of Health in Zoonosis, Small Animal Clinic, veterinary prescription control, rigorous control of the use of medicated feeds and the administration of antibiotics to promote growth in animals. Continuous training of health professionals and pharmacists. Well-funded research programmes aimed at finding alternative strategies to antimicrobials and antiviral drugs.

Supplementary List 4. Responses to question 8: If you believe any of these intervention/recommendations are not feasible in the Spanish context, please indicate which you believe are not feasible and provide rationale for why you do not believe it is feasible (i.e. due to culture, politics, geography, etc).

Political responsibility and coordination:

- Difficulty in making the political decision as organised in the framework of the AC
- I see them as feasible if politicians worked together for the common good.
- In the context of the health competencies distributed in the Devolved Regions, coordination is difficult. It should be centralised in a Crisis Committee with representatives of the Autonomous Regions in the Ministry of Health and dealt with in an Emergency Plan at national level.
- There should be specialists in Infectious Diseases in the national committee of experts.

Annex 4: Timeline and Evolution of Response to AMR in Spain and Beyond

