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# Stronger Bacteria Weaker Antimicrobial

In-depth analysis for the ENVI Committee



DIRECTORATE GENERAL FOR INTERNAL POLICIES  
POLICY DEPARTMENT A: ECONOMIC AND SCIENTIFIC POLICY

# Stronger Bacteria Weaker Antimicrobial

The fight against antimicrobial resistance in Europe through  
research, and the Andalusian PIRASOA program

## IN-DEPTH ANALYSIS

### Abstract

The research is the key to the fight against Antimicrobial Resistance, but funding against the AMR in Europe is not acceptable because of the magnitude of the health problem.

In this context, in Andalusia (Spain), the PIRASOA Programme has been successfully implemented and developed, integrated into the daily clinical practice. The preliminary outcomes show a reduction of antimicrobial consumption and antimicrobial resistance and an improvement of antimicrobial prescription profile. However, it is necessary to maintain professional motivation and more technical and human resources.

This in-depth analysis was commissioned by Policy Department A at the request of the Health Working Group of the Committee on the Environment, Public Health and Food Safety.

This document was requested by the European Parliament's Committee on Environment, Public Health and Food Safety

## **AUTHOR**

Dr. José Miguel CISNEROS

## **RESPONSIBLE ADMINISTRATOR**

Miklós László GYÖRFFI

## **EDITORIAL ASSISTANT**

Eva ASPLUND

## **LINGUISTIC VERSIONS**

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To contact the Policy Department or to subscribe to its newsletter please write to:  
Policy Department A: Economic and Scientific Policy  
European Parliament  
B-1047 Brussels  
[Poldep-Economy-Science@ep.europa.eu](mailto:Poldep-Economy-Science@ep.europa.eu)

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## LIST OF ABBREVIATIONS

<b>AMR</b>	Antimicrobial Resistance
<b>ASP</b>	Antimicrobial Stewardship
<b>ATM-AVI</b>	Aztreonam-Avibactam
<b>CR</b>	Carbapenem-resistant
<b>DDD</b>	Defined Daily Doses
<b>EU</b>	European Union
<b>HAIs</b>	Healthcare-associated infections
<b>ISCIII</b>	Instituto de Salud Carlos III
<b>MOOC</b>	Massive Online Open Course
<b>NI</b>	Nosocomial Infection
<b>ND4BB</b>	New Drugs For Bad Bugs
<b>PIRASOA</b>	Institutional Programme for the Prevention and Control of Healthcare Associated Infections and Appropriate Use of Antimicrobials
<b>OBD</b>	Occupied bed-days
<b>SAS</b>	Andalusian Health Service
<b>SSPA</b>	Andalusian Public Healthcare System
<b>UGCs</b>	Clinical Management Units

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## EXECUTIVE SUMMARY

### Background

- The research is key element to the fight against Antimicrobial Resistance (AMR). But, what is Europe's role in this task? What is the budget dedicated to research in Europe at European Union (EU) level or at national level? Are these actions enough?
- Europe is a world leader in AMR research through the launch of two programs: the New Drugs for Bad Bugs is the biggest public-private research partnership to combat AMR. This programme comprises 7 projects, focused at the development of new antibacterial drugs. The first projects kicked off in early 2013. The budget is around €700 million. The EU has also set up the Joint Programming Initiative on AMR with the objective of getting a better worldwide research efforts coordination. The budget is € 50 million.
- We can see two examples: REJUVENATE is a project included in COMBACTE-CARE. It is the first clinical trial of this initiative, whose goal is to evaluate the efficacy and safety of a new antimicrobial with activity against some carbapenem-resistant Enterobacteriaceae, “the worst bugs”. The project is in the final phase of patient recruitment. MagicBullet is a randomized, academic and multicenter clinical trial to compare the safety and efficacy of colistin vs. meropenem, for empirical treatment of ventilator-associated pneumonia. This project has been made possible thanks to the public funding of the European Commission through FP7, because colistin is an old antibiotic without commercial interest. The project is in the process of preparing manuscripts.
- The public funding for research on antibacterial resistance in Europe between 2007 and 2013 has been analyzed in this paper. It is interesting to underlying that of the total public investment in this period, 1.3 billion euros, 50.5% came from the EU, and only 49.5% from the JPIAMR countries. And also, there are significant variations in funding across countries. In the new European Action Plan against AMR of The European Commission, research remains a key objective. It says “Boosting research, development, and innovation on AMR” in seven specifics actions. However, multidrug-resistant (MDR) bacteria continue to spread and threaten with one million European citizens dead in 30 years. The funding against the AMR in Europe through research is not acceptable because of the magnitude of the health problem and this is not a resources problem since Europe is rich. The fight “against the ball” evidences it.
- In conclusion, I think that the leadership of the European Commission should be praised for the creation of ND4BB and the Joint Programming, for the amount of euros invested, and for the public-private nature of the initiative and the global dimension of the project. Also, I think that the research budget in AMR is not still enough, there are significant variations across countries and it does not take its rightful place within Europe's priorities.

### Aim

- I will expose you, my talk about the fight against antimicrobial resistance in Europe through research, and the Andalusian PIRASOA programme. Two examples of success still to be completed. The PIRASOA is the institutional programme for the Prevention and Control of Healthcare Associated Infections and Appropriate Use of Antimicrobials. All information is available in this internet link ([www.iavante.es/es/programa-pirasoa](http://www.iavante.es/es/programa-pirasoa)).



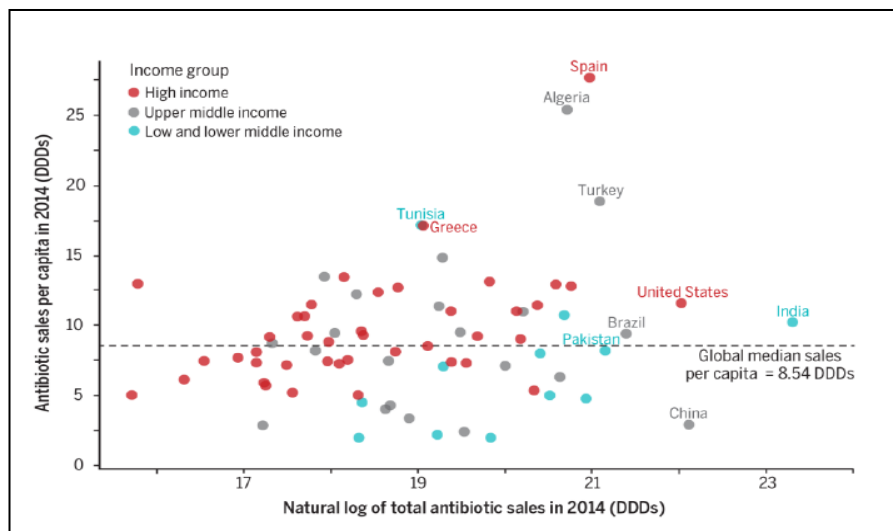
## GENERAL INFORMATION

### KEY FINDINGS

- PIRASOA programme has been implemented in a region of Spain to reduce the incidence of HAIs and to optimise the use of antibiotics until reaching the level of the best European countries.
- It is an education-based multifaceted programme with institutional support from the Andalusian Ministry of Health and Social Wellbeing, which is committed to be integrated into the daily clinical practice.

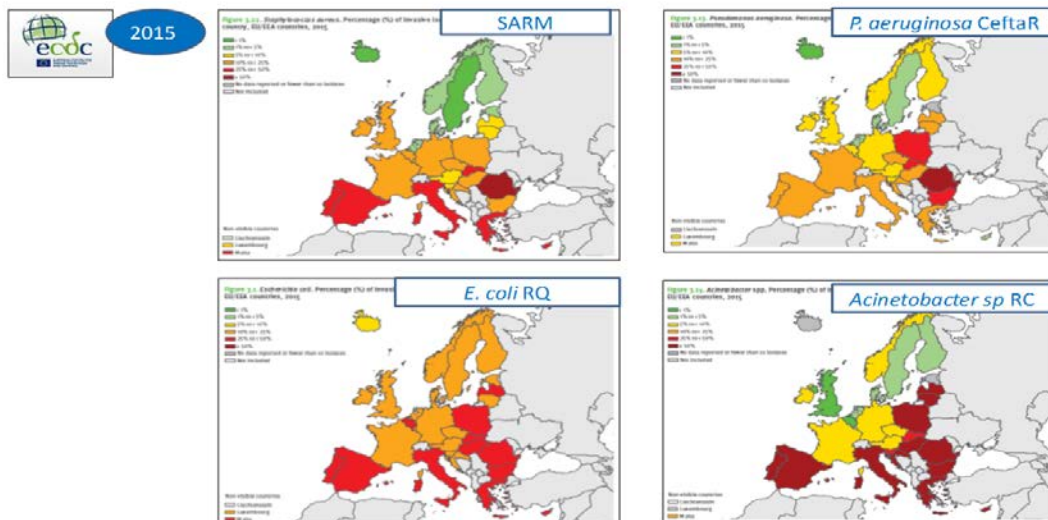
In the first place, as shown in Figure 1, it should be highlighted that Spain is in the top countries in the world in antimicrobial use. As a result, the bacterial resistance in Spain is higher than those in the northern European countries.

Figure 1: Antimicrobial use in the world.



Source: Laxaminarayan R et al. Science 2016

Figure 2: Bacterial resistance in Europe



Source: <https://ecdc.europa.eu/en/antimicrobial-resistance> (access 2 July 2017)

Spain has an action plan on AMR titled “National plan to fight antimicrobial resistance”, but the plan has no budget, no data, and it has not still results. Also, Spain, together with Belgium, Luxembourg and Cyprus, are the only countries without the specialty of infectious diseases. In this national scene, we have carried out the PIRASOA programme.

This is a quality clinical programme, it integrates both Healthcare Acquired Infections (HAIS) and Antimicrobial Stewardship Programmes (ASP), and the Primary Care and the Hospitals. It’s based on the professional leadership with institutional support.

The PIRASOA has two main objectives:

- To reduce the incidence of HAIs until reaching the level of the best European countries with the best indicators outcomes.
- To optimise the use of antibiotics until reaching the level of the best European countries with the best indicators outcomes.

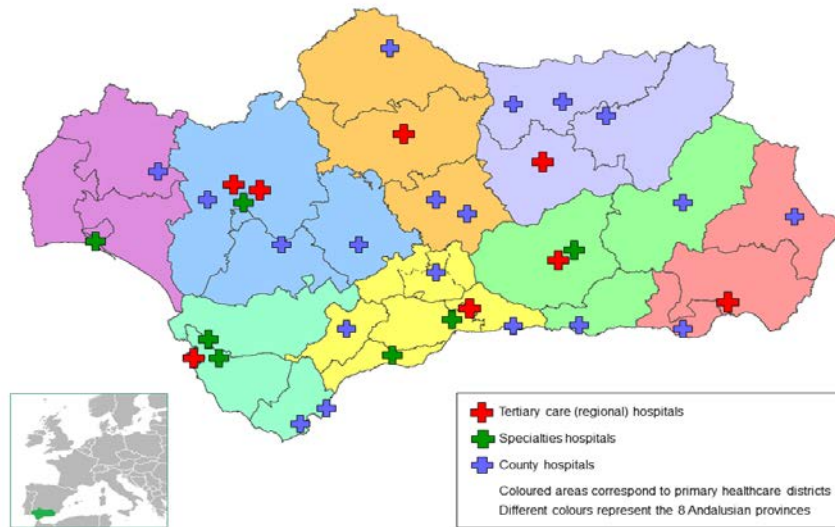
The programme has been carried out in Andalusia, which is the most populated region in Spain with 8.4 million inhabitants.

**Map 1: The setting: Andalucía**



The Andalusian Healthcare System is distributed in 34 hospitals (8 regional hospitals, 9 specialty hospitals, 17 county hospitals) and 27 primary care areas, with a 17182 physicians and a budget of 8683 million euros.

**Map 2: Andalusian Public Healthcare System (SSPA) hospitals and primary care settings**



Source: Author

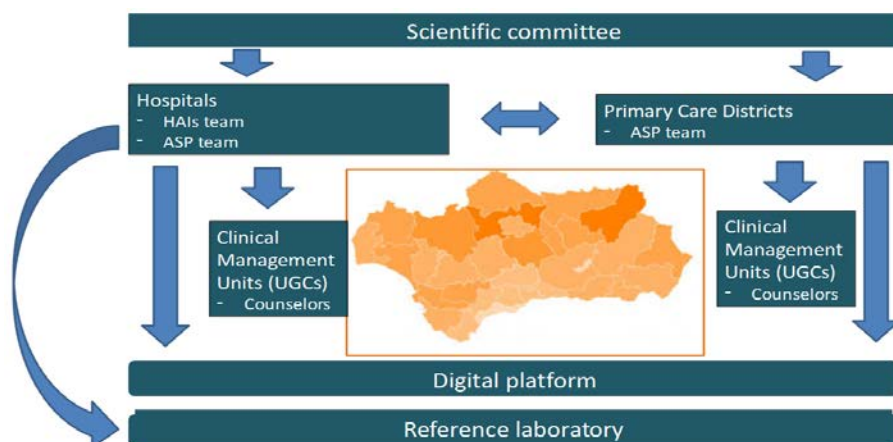
The structure and organisation of the programme are:

- The scientific committee is the main responsible for the program.
- In every hospital it has been created two multidisciplinary teams, one for HAIs and one for ASP. And one team for ASP in every Primary Care Area.
- Hospitals and primary care departments are the settings where the PIRASOA programme has to be performed as a part of routine clinical practice.

The PIRASOA programme has 2 common structures:

- The Digital Platform, with a free part, in which all documents including training material and periodic reports of results are kept and another encrypted that contains the database in which all the teams introduce their results.
- The other structure is the Reference Laboratory for Molecular Typing of Nosocomial Pathogens, where resistance mechanisms, main circulating clones and clonal relationships of nosocomial multidrug-resistant bacteria are investigated.

**Map 3: Structure and organisation of PIRASOA Programme**



Source: Author

The members of the Scientific Committee were selected from the scientific societies most involved in the prevention, diagnosis and treatment of infections and I have the honor and responsibility of being the director.

The PIRASOA has 638 healthcare professionals distributed in the 61 hospital and primary care teams. The teams have a multidisciplinary composition.

The programme contains 171 indicators about antimicrobial use (consume, quality of use, cost), resistance (incidence density of MDR bacteria in clinical samples), nosocomial infections (prevalence and incidence of NI) and clinical outcome (mortality of patients with bacteraemia). All the indicators have been selected based on the international standards.

Training is the key intervention of the programme and training tools included:

- Symposia, coinciding with the European Day of Antibiotics.
- Training Courses based on the Massive Online Open Course methodology, almost 7000 healthcare professionals have taken the courses.
- Updated of the local guides for antimicrobial therapy.
- Feedback was provided to every center by quarterly reports (13 until now).
- Educational interviews, which are the main activity of the ASP. Since the beginning of the program, 80000 EI have been conducted. The methodology of the EI has been previously described by us and successfully implemented in a hospital setting.

The programme has enjoyed strong institutional support:

- It is an official program of Andalusian Health Service.
- It is included in the management agreements between the SAS, the centers, and the departments.
- Specific budget for reference Laboratory.
- Presentation in the Andalusian Parliament by the regional Health Ministry Signing of the PIRASOA agreement official councils of doctors, pharmaceuticals and dentists.

## SUMMARY OF RESULTS OF PIRASOA PROGRAMME

### KEY FINDINGS

- The quality of the use of antimicrobial agents has improved along the programme.
- The total antibiotic consumption in both primary care and hospitals was reduced.
- The MDR bacteria did not increase during the programme.
- The programme has achieved resources to research in competitive call

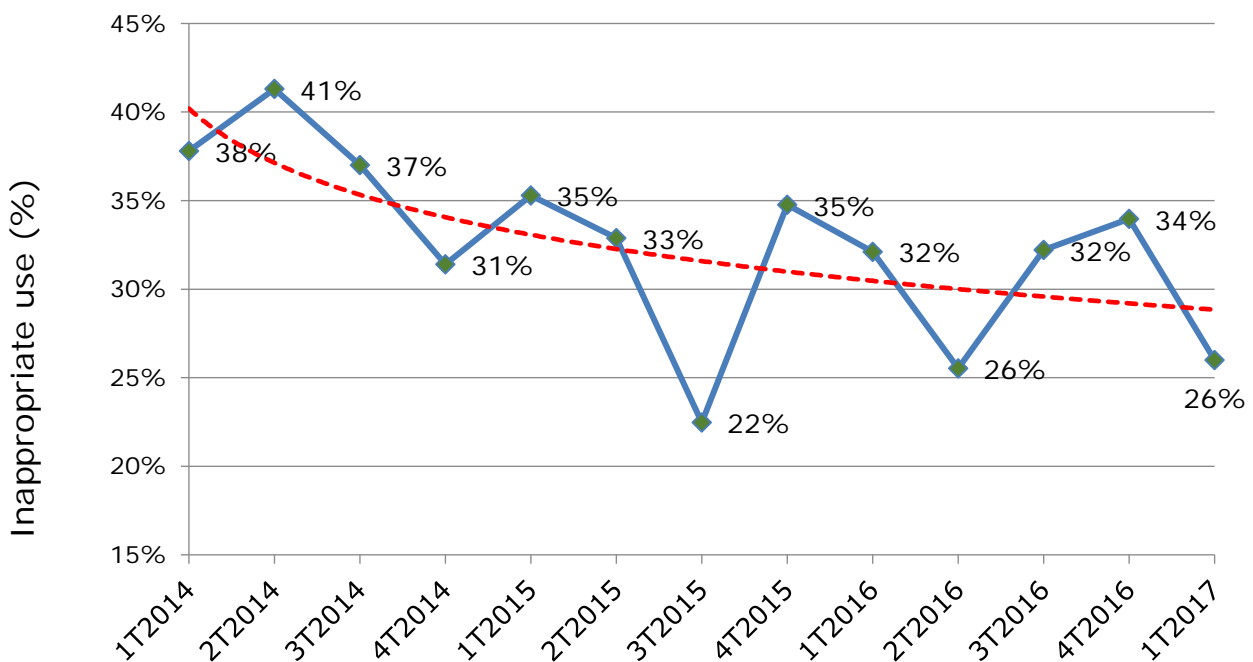
Here you will find the summary of the results achieved by The PIRASOA programme since January 2014 to march/June 2017

### 1.1. Results of PIRASOA Programme in Hospitals

#### 1.1.1. Quality of the use of antimicrobial agents

- The graph shows the quarterly evolution of the rate of inappropriate antimicrobial use based in the evaluation by educational interviews. From 38% at the beginning of the programme to 26% in the last quarterly.

**Figure 3: Inappropriate antimicrobial use rate (%)**

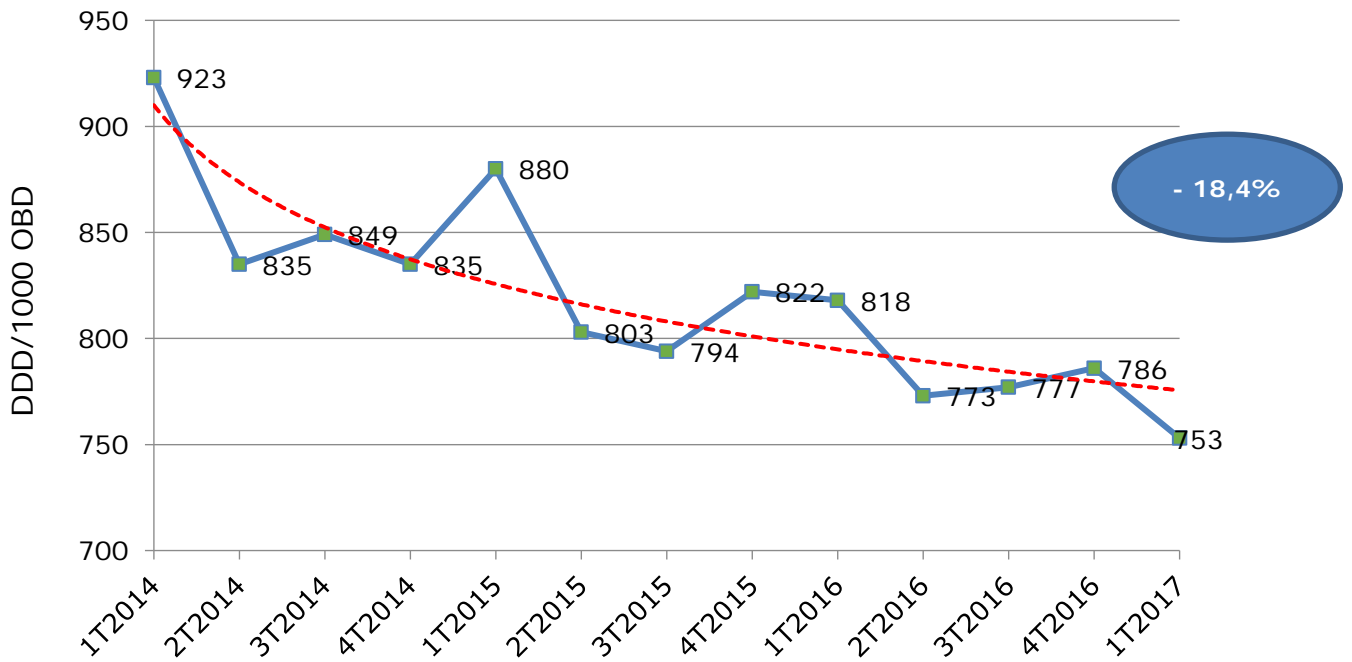


Source: Author

#### 1.1.2. Antibiotic consumption

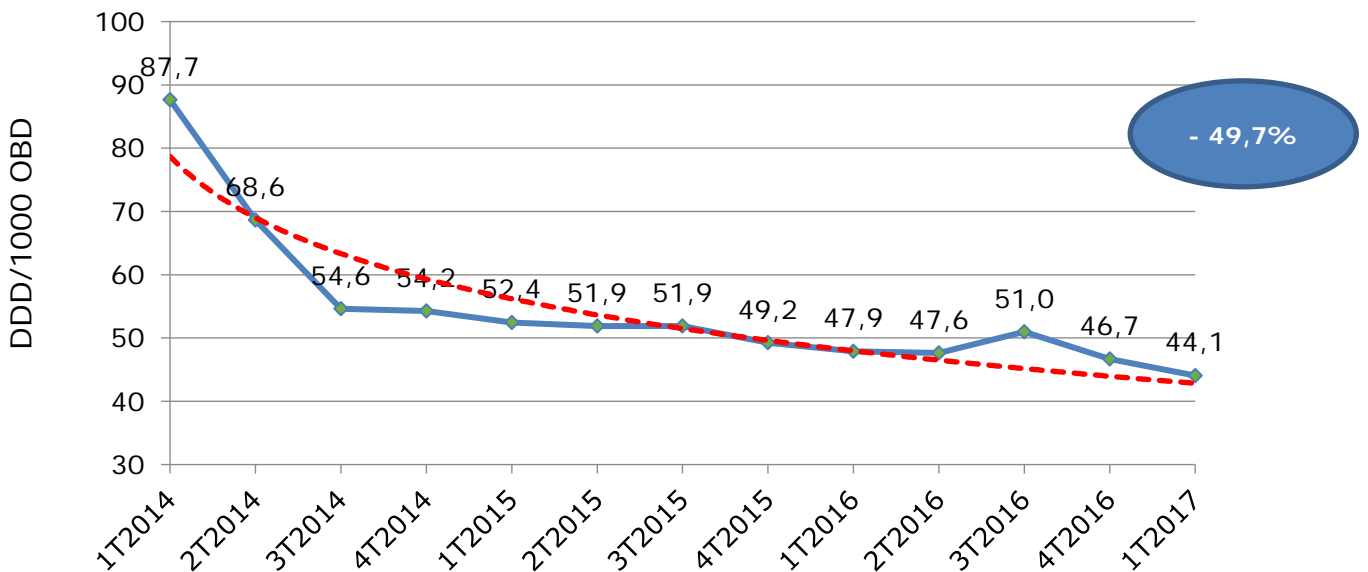
- The antibiotic consumption in the hospital was reduced by 18.4%, from 923 DDD/1000 OBD in the first quarterly of 2017 to 753 in the same period of 2017.
- The carbapenem consumption was reduced by 50%.

**Figure 4: Antibiotic consumption in hospitals**



Source: Author

**Figure 5: Carbapenem consumption in hospitals**

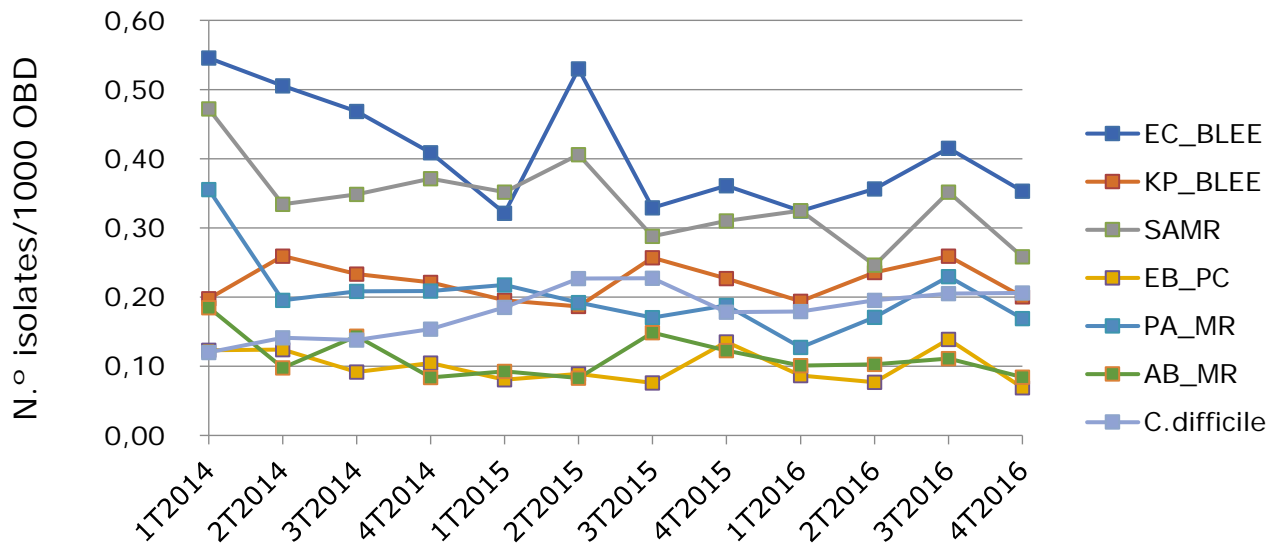


Source: Author

### 1.1.3. Bacterial resistance

- The MDR bacteria did not increase during the programme. The graph shows the quarterly evolution of the different bacteria monitored.
- Fortunately the evolution of enterobacterial CR infections/colonizations in the hospital show a decrease to compare the first quarter with the last.

**Figure 6: Evolution of the incidence of MDR bacteria**



Source: Author

**Figure 7: Evolution of enterobacterial CR infections/colonizations**

1T 2014

4T 2016

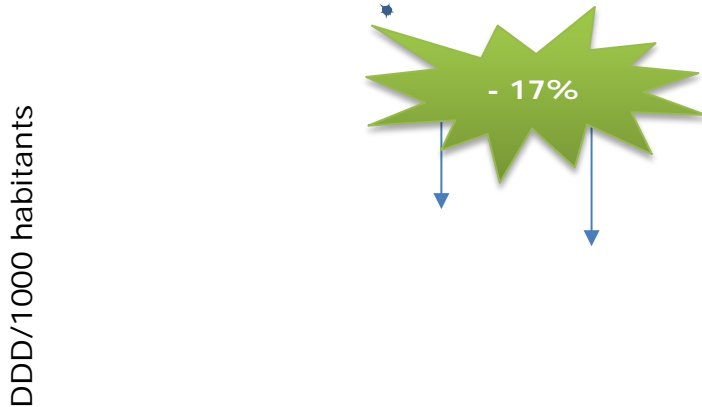
Source: Author

## 1.2. Results of PIRASOA Programme in Primary Care

### 1.2.1. Antibiotic consumption

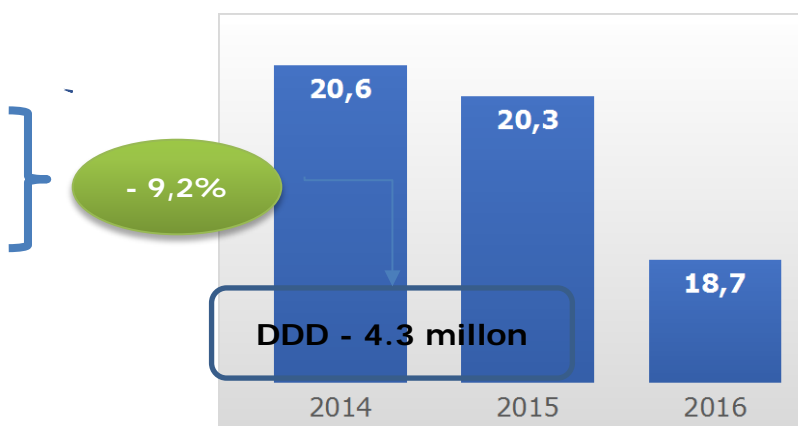
- In primary care, the antibiotic consumption was reduced by 17%. 21.6 DDD/1000 HD in the second quarter of 2014 to 16.5 in the same period of 2017 and between 2015 and 2016 the antibiotics consumption in primary care was reduced by 9.2%, that meanings a global reduction of 4.3 million DDD yearly.

**Figure 8: Antibiotic consumption in primary care**



Source: Author

**Figure 9: Annual antibiotic consumption in primary care**

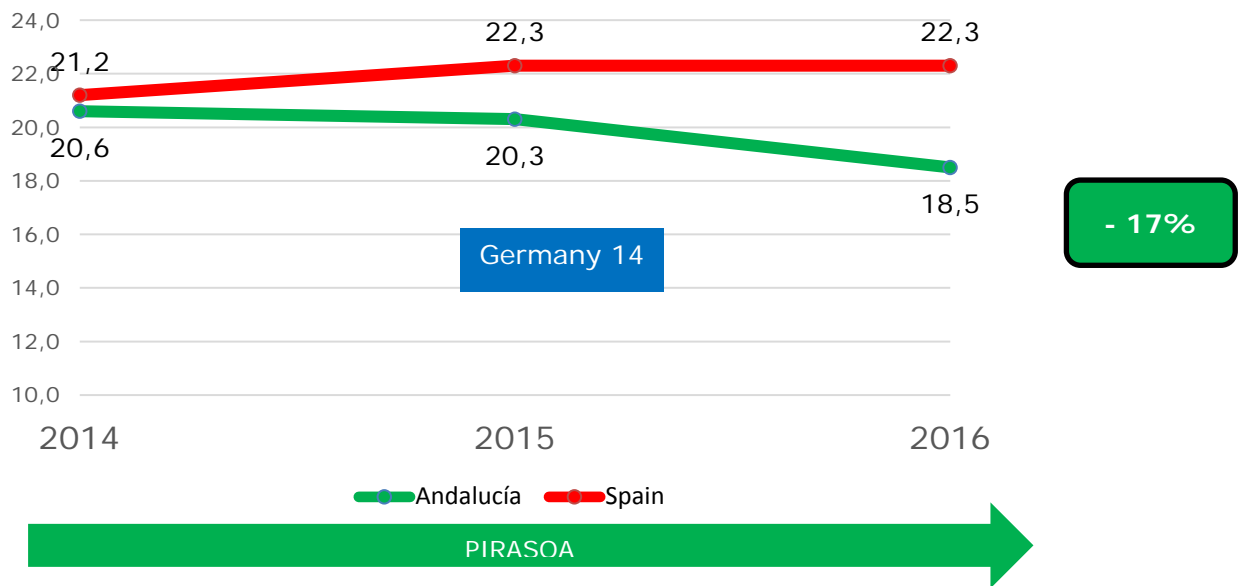


Source: Author

- These figures are more impressive taken account that in Spain, in the same period, the antibiotics consumption. But it is still far to Germany data.



**Figure 10: Antibiotic consumption in primary care: Andalucía vs. Spain**



Source: Author

- The amoxicillin/clavulanic consumption in primary care, the antibiotic with higher impact in outpatient, was reduced by 37%. 8.7 DDD/1000 hab.day in the second quarter of 2014 to 5.5 in the same period of 2017.

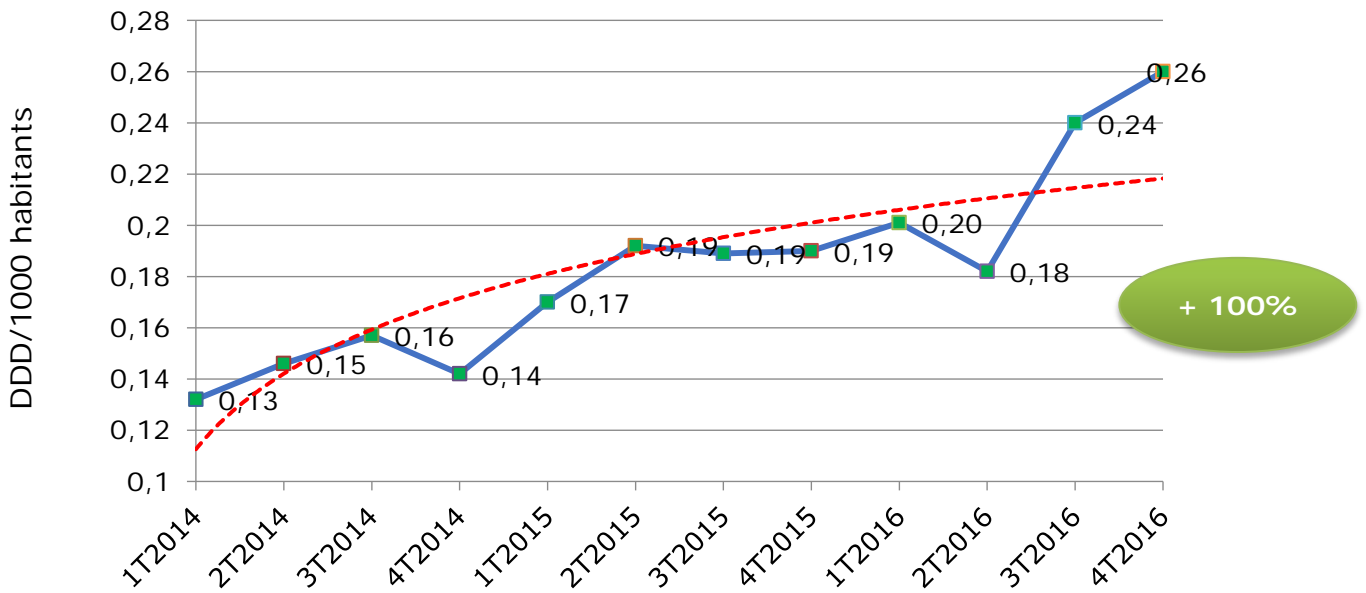
**Figure 11: Amoxicilin/clavulanic consumption in primary care**



Source: Author

- In the opposite, the consumption of fosfomicin-trometamol in primary care was increased by 100%.
- These profound and sustained changes of antibiotics consumption and profile prescription in primary care, have an ecological impact.

**Figure 12: Fosfomicin-trometamol consumption in primary care**

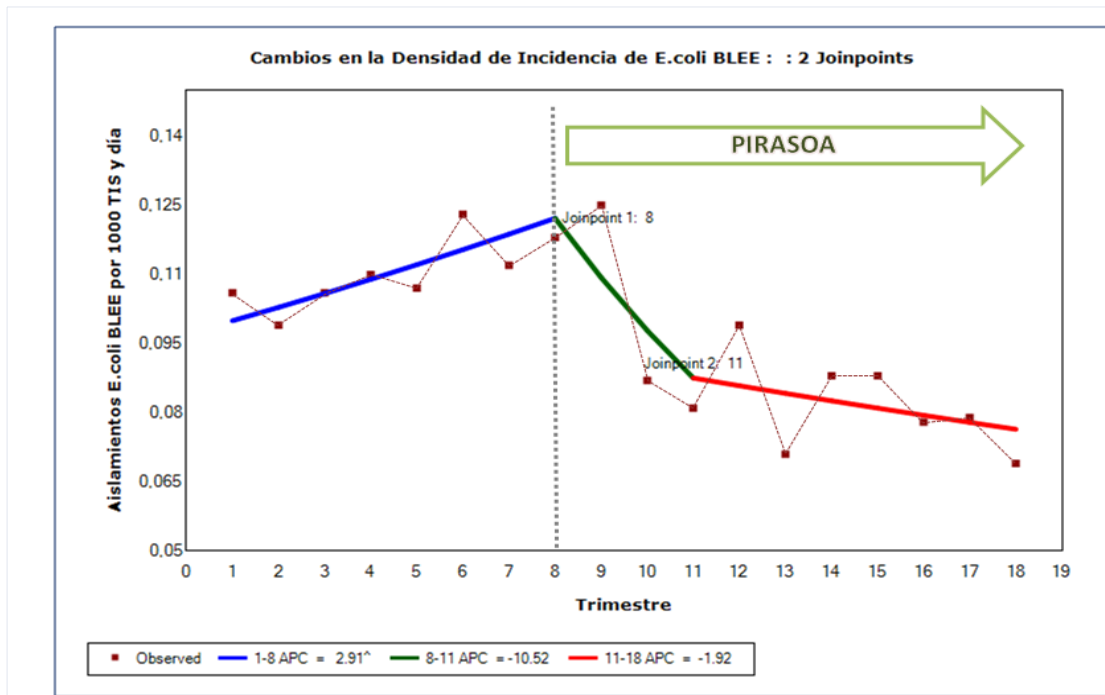


Source: Author

1.2.2. Bacterial resistance

- The graph shows the evolution of incidence of *Escherichia coli* producing extended-spectrum beta-lactamases in clinical samples. You can see a significant increase in the pre-PIRASOA period and a significant reduction in the PIRASOA period.

**Figure 13: Incidence of *E. coli* ESBL in clinical samples in Primary Care**



### 1.3. Research

- Finally, the programme has achieved resources to research in competitive call from Spanish Health Ministry, from the SEIMC, and in the last call to European Joint Action, with the project "Develop and test near real time surveillance of antimicrobials and multidrug resistant bacteria".

## CONCLUSIONS

The PIRASOA programme has been successfully implemented and developed. The preliminary outcomes show:

- Reduction of antimicrobial consumption.
- Improvement of antimicrobial prescription profile.
- Reduction of microbial resistance.
- Funding for research.

The PIRASOA Programme needs:

- Maintain professional motivation.
- Add to current institutional support technical and human resources.
- Specifics plan for nursing homes.
- To disseminate the results.

The PIRASOA programme has been possible thanks to a great team-work, in which I want to highlight the 638 professionals that, integrated into the HAIs and ASP local teams have carried out the most important field-work.

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## NOTES

Competing interests: I work as a doctor for Andalusian Health Service. I received funding for research in AMR from the Spanish Ministry of Health and the European Commission and grant from these pharmaceuticals companies: Novartis, Astellas, Pfizer, MSD, Janssen and Astra-Zeneca.

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